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THE SYNDROME OF THE SUPERIOR CEREBELLAR ARTERY AND ITS BRANCHES

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Cerebellar vascular insults, in contrast to cerebral vascular occlusions, are rare. In this respect disease of the vessels of the cerebellum is almost as uncommon as disease of the vessels of the spinal cord. Of three hundred cases of cerebral vascular insults in which autopsy was performed, in only twenty was there evidence of involvement of the cerebellar vessels. The pathologic process in nine of these cases was confined to the superior cerebellar artery or its branches.

The nature of the vascular supply of the cerebellum explains the rarity of cerebellar occlusion. As is well known, the surface of the cerebellum, in contrast to that of the cerebrum, presents a more liberal anastomosis of the blood vessels. It should also be emphasized that the cerebral and cerebellar vessels are not end-arteries as was once stated by Cohnheim, Duret and others. As demonstrated by Pfeifer,[1] Cobb[2] and others, there is a perfect anastomosis of the capillary beds of the cerebellar vessels in both the gray and the white matter. Clinical evidence of involvement of the cerebellum as a result of thrombosis of its vessels cannot always be elicited, for several reasons: (1) failure of small lesions of the cerebellum to produce symptoms, because the free anastomosis between the cerebellar arteries prevents softening in many cases of occlusion of one or more of their branches; (2) masking of the cerebellar signs because of frequently associated massive cerebral vascular occlusions; (3)

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1. Pfeifer, R. A.: Die Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928.

2. Cobb, S.: The Cerebral Circulation: XIII. The Question of "End Arteries" of the Brain and the Mechanism of Infarction, Arch. Neurol. & Psychiat. **25**:273 (Feb.) 1931.

dominance of one part of the cerebellum over another, or of one entire hemisphere over the other and compensation by new assumption of function, and (4) individual variability of the area irrigated by a certain vessel. In order to facilitate an understanding of the lesions and their anatomic relations, a brief description of the vascular supply of the cerebellum will be given. The superior cerebellar artery only will be described in detail. It was found advisable to follow the more recent nomenclature of the divisions of the cerebellum as described by Bolk,[3] Ingvar[4] and Riley.[5]

THE VASCULAR SUPPLY OF THE CEREBELLUM

The cerebellum is supplied by three main arteries: the superior cerebellar, the anterior inferior cerebellar and the posterior inferior cerebellar. French authors have called the latter two the middle and inferior cerebellar arteries. Some authors have described a fourth artery, the middle inferior cerebellar artery. The superior and anterior inferior cerebellar arteries originate from the basilar artery. The posterior inferior cerebellar artery springs from the vertebral artery; at times it originates on one side from the vertebral and on the other side from the basilar artery. Anomalies of the cerebellar vessels are frequent. The anterior inferior cerebellar artery may be totally absent or may originate from the vertebral or posterior inferior cerebellar artery. Of the three cerebellar vessels the superior cerebellar artery is the most constant. One case of its absence was reported by Stopford,[6] and Longo[7] quoted another instance. In these cases the posterior cerebral artery supplied the respective parts of the cerebellum. Blackburn,[8] on examining two hundred and twenty cases, found the superior cerebellar artery present in all patients.

The Superior Cerebellar Artery.—This arises from the basilar artery near its origin. It passes laterally into the upper border of the pons and runs parallel to the posterior cerebral artery; it is separated from the latter by the oculomotor nerve. After turning around the lateral side of the cerebral peduncles it reaches the cerebellum and divides into two branches, a medial and a lateral branch, which supply the superior surface of the cerebellum (fig. 1). The

3. Bolk, L.: Das Cerebellum der Säugetiere, Jena, Gustav Fischer, 1906.

4. Ingvar, S.: Zur Phylo- und Ontogenese des Kleinhirns, Folia neuro-biol. **11**:205, 1919.

5. Riley, H. A.: The Lobules of the Mammalian Cerebellum and Cerebellar Nomenclature, Arch. Neurol. & Psychiat. **24**:227 (Aug.) 1930.

6. Stopford, J. S. B.: The Arteries of the Pons and Medulla Oblongata, J. Anat. **50**:151; **51**:252, 1916.

7. Longo, L.: Le anomalie del polygono di Willis dell'uomo studiate comparativamente in alcuni mammiferi ed ucelli, Anat. Anz. **27**:170 and 200, 1905.

8. Blackburn, J. N.: Anomalies of Encephalitic Arteries Among the Insane, J. Comp. Neurol. **17**:493, 1907.

artery has been found frequently to supply a few irregular branches to the pons and to some of the structures of the mesencephalon, such as a part of the nucleus ruber and substantia nigra. Alezais and d'Astros [9] have shown that branches are also given off to the inferior colliculi and to the lateral and cephalic parts of the brachium pontis. Occasionally, branches also supply the cerebral peduncles (Alezais and d'Astros [9]) or the middle cerebellar peduncles.

The two main branches, as already stated, are the medial and the lateral. The medial branch runs to the surface of the cerebellum, where

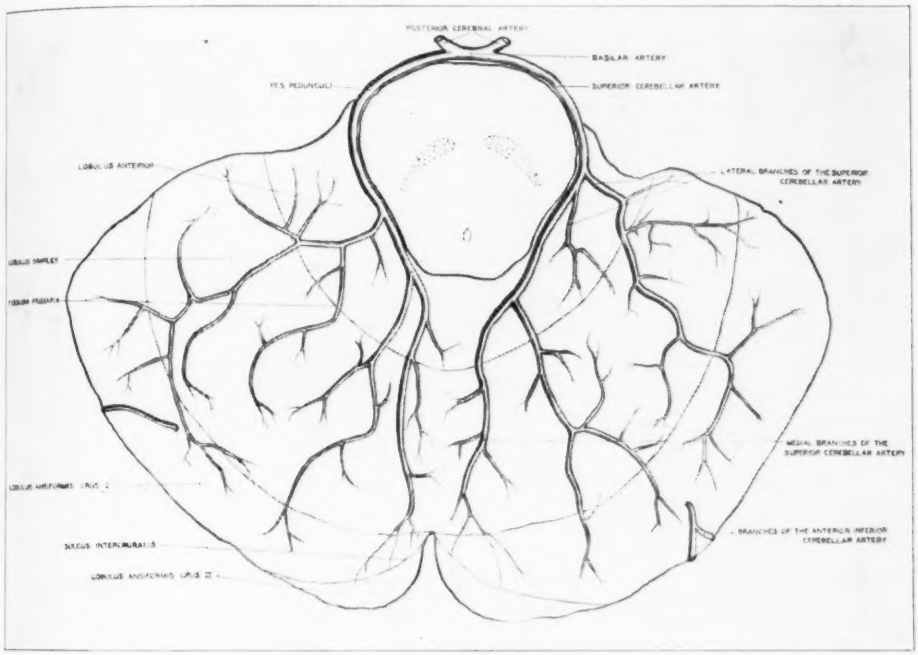

Fig. 1.—Distribution of the superior cerebellar artery on the superior surface of the cerebellum, supplying the lobulus anterior, lobulus simplex and lobulus ansiformis crus 1, as well as the upper part of the vermis (lobulus II, lobulus IV and lobulus C_2).

it ends in two or three branches (fig. 1). The more medially situated branches supply the upper parts of the vermis up to the tuber vermis (lobulus II vermalis, lobulus IV vermalis and lobulus C_2 vermalis [presulcal], fig. 1). Parts of the mesial surface of the lobulus anterior, simplex and ansiformis (crus 1) are also supplied by collaterals of the mesial branch (fig. 1). These two mesial branches form a free anastomosis in the region of the vermis. The lateral branch supplies the

9. Alezais and d'Astros: La circulation artérielle du pédoncule cérébral, J. de l'anat. et de la physiol. **28**:519, 1892.

remainder of the superior surface of the cerebellar hemispheres (lobulus anterior, simplex and ansiformis, crus 1, fig. 1) up to the sulcus intercruralis (great horizontal fissure), where it anastomoses with the anterior inferior cerebellar artery. A lateral branch is given off to the anterior surface of the cerebellar hemisphere and a basal lateral branch to the lateral anterior part of the cerebellum up to the flocculus.

The two main branches send numerous collaterals to the deeper parts supplying the anterior medullary velum, quadrigeminal plate, choroid plexus of the fourth ventricle, cerebral peduncles, pons, brachium conjunctivum, brachium pontis and deep white matter of the cerebellum. The superior cerebellar artery is also the main arterial supply to the inner cerebellar nuclei, especially the dentate nucleus. The last named is also supplied in part by the anterior inferior cerebellar artery. Shellshear [10] claimed that the blood supply to this nucleus comes from the posterior inferior cerebellar artery. The observations of most authors and the findings in our nine cases do not substantiate this opinion.

The vessels of the cerebellum should be classified further into two groups: the superficial and the deep cerebellar arteries. The superficial arteries are short collaterals of the pial branches and supply essentially the cortex of the cerebellum. They are subdivided into branches which irrigate: (1) the molecular layer; (2) the molecular layer and the Purkinje cell and nuclear cell layers, and (3) the nuclear cell layer and the white matter. The branch irrigating the nuclear cell layer and the white matter anastomoses with the deeper branches. The deep branches enter, in the form of large collaterals of the pial vessels, deep into the fissure when they penetrate the single cerebellar lamellae supplying (1) the white matter only and (2) the white matter and the nuclear cell and Purkinje cell layers. The molecular layer and the Purkinje cell layer are supplied essentially by the superficial arteries, while the nuclear cell layer and the white matter are irrigated essentially by the deeper branches.

NOMENCLATURE OF THE CEREBELLAR LOBES

The following nomenclature [11] of the cerebellar lobes and vermis was adopted. The older nomenclature is inserted in parenthesis:

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10. Shellshear, J. L.: Blood Supply of the Dentate Neucleus of the Cerebellum, Lancet **1**:1046, 1922.

11. This classification differs slightly from that of Riley in that each lateral lobule of the cephalic lobe is called lobulus anterior. The caudal lobe is divided into six parts, instead of five, by the subdivision of the ansiform lobe into the lobulus simplex and the lobulus ansiformis, crus 1 and crus 2. This classification might be further simplified by calling all the structures between the fissura primaria and secunda the medial lobe and the lobulus paraflocculari and flocculari the posterior lobe.

CEPHALIC LOBE

Vermis	*Cerebellar Hemispheres*
Lobulus I vermalis (Lingula)	
Lobulus II vermalis (Lobulus centralis)	Lobulus anterior
Lobulus IV vermalis (Culmen)	

Fissura Primaria

CAUDAL LOBE

Lobulus C_2 vermalis, presulcal (Clivus) (Folium vermis)	Lobulus simplex
	Lobulus ansiformis crus 1 (Lobulus semilunaris superior)

Sulcus Intercruralis

(*Great Horizontal Fissure*)

Lobulus C_2 vermalis, postsulcal (Tuber valvulae)	Lobulus ansiformis crus 2 (Lobulus semilunaris inferior) (Lobulus gracilis)
Lobulus C_1 vermalis (Pyramis)	Lobulus paramedianus (Lobulus biventer)

Fissura Secunda

Lobulus B vermalis (Uvula)	Lobulus paraflocularis (Tonsil)

Fissura Paraflocculo-Floccularis

Lobulus A vermalis (Nodulus)	Lobulus floccularis (Flocculus)

REPORT OF CASES

For the purpose of study sections of the cerebellum in the area of softening as well as sections above and below the lesions were embedded and stained by the myelin sheath and cresyl violet methods.

CASE 1.—*Complete occlusion of the left superior cerebellar artery; signs of cerebellar involvement on the left side and sensory disturbances on the right; destruction of the brachium conjunctivum, the descending mesencephalic root of the fifth nerve, part of the medial lemniscus, the lobulus anterior, lobulus simplex and lobulus ansiformis crus 1 and part of the cerebellar nuclei on the left side.*

History.—M. A., a man aged 40, a furrier, was admitted to the Montefiore Hospital on Dec. 19, 1931. He complained of occasional attacks of shortness of breath and weakness of two years' duration. In April 1931, after a diagnosis of mitral stenosis and insufficiency was made, he gave up his work. On Aug. 15, 1931, he had an attack of unconsciousness accompanied by convulsions and vomit-

ing. Examination made at the Mount Sinai Hospital disclosed an enlargement of the heart to the left with auricular fibrillation and a blood pressure of 118 systolic and 80 diastolic.

Neurologic Examination.—There were: bilateral horizontal nystagmus; slow, drawling speech; a broad-based gait; a Romberg sign; signs of cerebellar involvement on the left side, and impairment of sensation to touch, pain and temperature on the entire right side of the body, which was most evident in the lower dermatomes. All other forms of deep sensibility were preserved. A diagnosis of embolism of the left superior cerebellar artery was made. The sensory disturbances and signs of cerebellar involvement subsided somewhat, and the patient was discharged from the hospital. The condition remained stationary until Dec. 18, 1931, when another cerebral accident occurred and the patient became aphasic. Neurologic examination at this time disclosed: right hemiplegia with aphasia, apraxia, signs of cerebellar involvement on the left side, and a Babinski sign and spinothalamic sensory disturbances on the right side.

Course.—On March 2, 1932, the patient had another acute cerebral insult, resulting in complete aphasia and flaccidity of the right extremities. He died on May 10, 1932, after a pulmonary infection.

Laboratory Data.—Tests gave negative results.

Clinical and Anatomic Diagnosis.—The diagnosis was: emboli in the left middle cerebral and the left superior cerebellar artery; chronic rheumatic endocarditis, and mitral stenosis and insufficiency.

Autopsy.—Gross Examination: There was an area of softening along the distribution of the left middle cerebral artery, with destruction of the precentral, postcentral, parietal, superior and inferior temporal, insular, angular and supramarginal convolutions. In addition, the superior surface of the entire left hemisphere of the cerebellum was softened. The following convolutions of the left cerebellar hemisphere were affected: the lobulus anterior, lobulus simplex and lobulus ansiformis crus 1. The cerebellum and pons were cut coronally. In addition to the aforementioned lesions, there was softening of the brachium conjunctivum, the nucleus dentatus and nucleus emboliformis and part of the brachium pontis. Only the lateral part of the vermis was involved.

Microscopic Examination: In a section through the brachium conjunctivum, the fourth ventricle and the upper part of the cerebellum there was destruction of the left lobulus anterior and the brachium conjunctivum (fig. 2*A*). The brachium pontis, Gowers' tract, the descending mesencephalic root of the fifth nerve, the lateral lemniscus and the lateral part of the medial lemniscus on the left side were partially demyelinated. There was also slight involvement of the lateral parts of the lobulus II vermalis and lobulus IV vermalis (fig. 2*A*). In a section of the cerebellum and medulla oblongata through the nuclei of the tenth and twelfth nerves (fig. 2*B*) there was destruction of the lobulus simplex and lobulus ansiformis crus 1. As can be seen from the figure, the lobulus C_2 vermalis, which forms part of the lobulus simplex, was slightly involved on the left lateral surface (fig. 2*B*). The lobulus C_1 vermalis and lobulus B vermalis were intact. The upper two thirds of the left dentate nucleus were shrunken and destroyed (fig. 2*B*). The left globose, fastigial and emboliform nuclei were likewise destroyed. With higher magnification it was seen that the white fibers of the lobulus C_2 vermalis on the left did not take the myelin stain as well as did those on the right. There were descending demyelinization of the left pyramid of the medulla oblongata and slight hypertrophy and paling of the right inferior olivary nucleus (fig. 2*B*). The right thalamo-olivary bundle stained poorly.

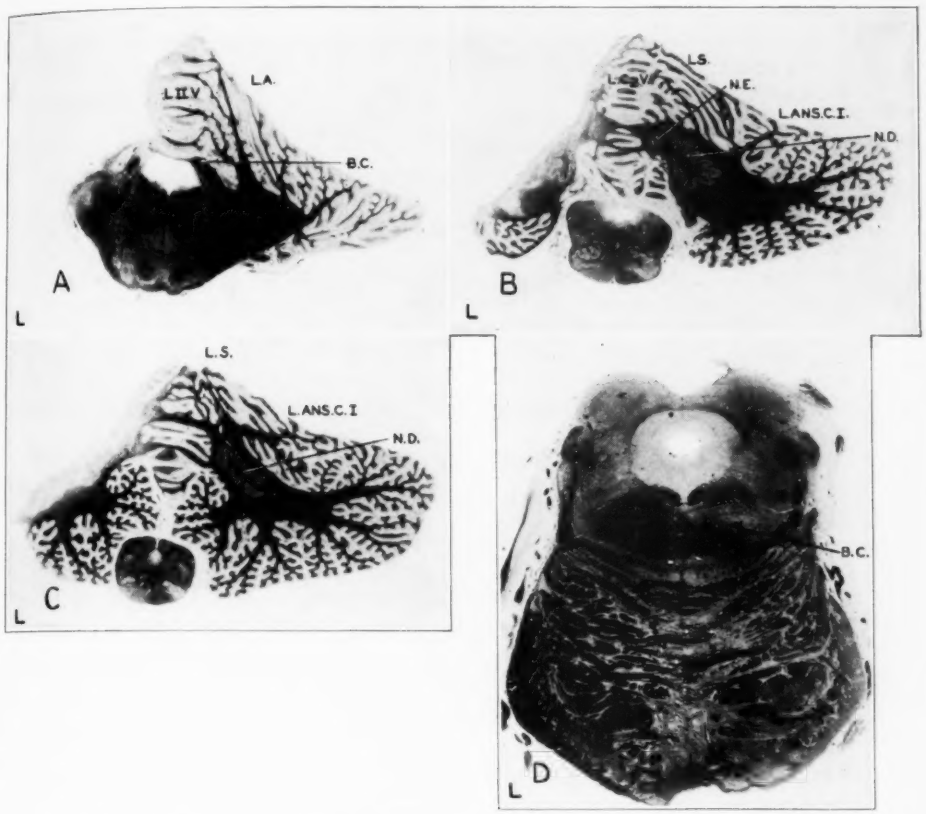

Fig. 2 (case 1).—*A*, coronal section of the pons and cerebellum through the fourth ventricle, showing destruction of the left lobulus anterior (*L.A.*), brachium conjunctivum (*B.C.*) and descending mesencephalic root of the fifth nerve and part of the brachium pontis. Notice the slight involvement of the lateral part of the lobulus II vermalis (*L.III.V.*). *B*, coronal section through the cerebellum and medulla oblongata, showing destruction of the left lobulus simplex (*L.S.*) and lobulus ansiformis crus 1 (*L.Ans.C.I.*), dentate nucleus (*N.D.*) and emboliform nucleus (*N.E.*). The lobulus C_2 vermalis (*L.C*$_2$*V.*) is slightly implicated. The demyelinization of the left pyramid is a descending demyelinization from the lesion in the left cerebral hemisphere. Notice the pale and hypertrophied right inferior olivary nucleus. *C*, same section as that shown in figure 2 *B*, passing through the nuclei gracilis and cuneatus and showing destruction of the lobulus simplex (*L.S.*), lobulus ansiformis crus 1 (*L.Ans.C.I.*) and dentate nucleus (*N.D.*). The right inferior olivary nucleus is hypertrophied. *D*, section through the decussation of the brachia conjunctiva, showing ascending demyelinization of the right brachium conjunctivum (*B.C.*). Myelin sheath stain.

With a higher magnification the ganglion cells of the upper two thirds of the dentate nucleus were seen to be destroyed; they were replaced by compound granular corpuscles and glia cells.

In a section through the dentate nucleus and medulla oblongata in the region of the cuneate and gracile nuclei (fig. 2*C*) there was destruction of the lobulus ansiformis crus 1. As is readily seen from the section, the lobulus ansiformis crus 2 was spared. In addition, there were destruction of the left dentate nucleus and nucleus emboliformis, hypertrophy of the right inferior olivary nucleus and descending demyelinization of the left pyramid (fig. 2*C*). In a section farther down the same process was observed.

A section of the mesencephalon through the nucleus of the fourth nerve showed demyelinization of part of the right brachium conjunctivum (fig. 2*D*). There was also slight demyelinization of the left lateral lemniscus (ascending degeneration). In a section through the red nuclei the right red nucleus and its capsular fibers did not take the stain as well as the left. This was the result of an ascending degeneration of the brachium conjunctivum. There was also descending demyelinization of the pes pedunculus as a result of the cerebral lesion.

Sections of the spinal cord disclosed descending demyelinization of the right lateral pyramidal tract.

Comment.—The first lesion in this case was caused by obstruction of the superior cerebellar artery by an embolus, with the typical syndrome following such occlusions. Some time later another embolus blocked the left middle cerebral artery. As a result of the complete closure of the superior cerebellar artery there was softening of the lobulus anterior, lobulus simplex and lobulus ansiformis crus 1. In addition, there was destruction of the brachium conjunctivum, the lateral lemniscus, the mesencephalic root of the fifth nerve, the lateral part of the medial lemniscus and the dentate, emboliform and globose nuclei on the left. There was also partial destruction of the brachium pontis. This structure is partially supplied by the superior cerebellar artery. The lateral parts of the lobulus II vermalis and lobulus IV vermalis, which are supplied by the mesial branch of the superior cerebellar artery, were slightly involved. The anastomoses from the mesial branches of the right superior and other cerebellar arteries most likely account for the sparing of the vermal portion of the cerebellum.

CASE 2.—*Complete occlusion of the left superior cerebellar artery; signs of cerebellar involvement on the left side; sensory disturbances on the right. Destruction of the brachium conjunctivum, the spinothalamic tract, part of the brachium pontis, the lobulus anterior, the lobulus simplex, the lobulus ansiformis crus 1 and part of the lobulus ansiformis crus 2 and the cerebellar nuclei on the left.*

History.—M. H., a man aged 44, was admitted to the hospital on Sept. 10, 1927. In March 1926 he had had an attack of dizziness, vomiting and severe headache. He consulted a physician, who noted weakness of the right arm and leg and a systolic blood pressure of 220.

Neurologic Examination.—The disks were somewhat pale, and the vessels of the fundi showed moderate atherosclerotic changes. There was a right homonymous hemianopia. There was ptosis on the left side with narrowing of the palpebral fissure without any other evidence of involvement of the third nerve. The left

extremities were hypotonic and showed an impairment of motor power. There were disturbances in coordination, ataxia, intention tremor and adiadokokinesis on the left. All the deep reflexes were diminished on the left. The left knee jerk was pendulous. There were a Babinski sign and allied responses on the right. There was diminution in sensations to pinprick and to heat and cold on the entire right side of the body; other forms of sensation were unimpaired. Except for some facetiousness, mental examination gave negative results.

Course.—On Dec. 16, 1928, while the patient was in the bathroom he lost consciousness. Examination immediately after the attack of unconsciousness disclosed: stupor, rigidity of the neck, flaccidity of the upper and lower extremities on the right side, decrease in the reflexes on the right and absence of abdominal reflexes. Fluid obtained by spinal tap was tinged with blood. The patient died on Dec. 20, 1928.

Laboratory Examinations.—The blood pressure was 230 systolic and 140 diastolic. The Wassermann reaction of the blood was negative. The spinal fluid was under normal pressure and was filled with red blood cells.

Clinical and Anatomic Diagnosis.—The diagnosis was cerebral arteriosclerosis, thrombosis of the left superior cerebellar artery and hemorrhage from the branches of the right middle and posterior cerebral arteries.

Autopsy.—Gross Examination: The cerebral vessels showed atherosclerotic changes. The cerebrum and cerebellum were cut horizontally. There was a hemorrhagic area in the left hemisphere involving the caudate nucleus, putamen, posterior limb of the internal capsule, pulvinar, lateral nuclei of the thalamus, globus pallidus, substantia nigra and red nucleus. This hemorrhage had broken into the lateral ventricle. An additional old area of softening had destroyed the greater part of the superior surface of the left hemisphere of the cerebellum and the left dentate nucleus and brachium conjunctivum.

Microscopic Examination: A complete horizontal section of the brain and cerebellum through the red nuclei disclosed a recent hemorrhage along the course of the middle and posterior cerebral arteries; it had destroyed the greater part of the subcortex, as previously stated. The oculomotor nerve fibers were also implicated (fig. 3*A*). In the same section almost the entire left cerebellar hemisphere was destroyed (fig. 3*A*), the destruction involving the lobulus anterior, lobulus simplex and lobulus ansiformis crus 1. The extreme left lateral parts of the lobulus II vermalis, lobulus IV vermalis and lobulus C_2 vermalis (presulcal) were also slightly involved (fig. 3*A*); the central parts of the vermis were intact. Sections cut slightly below this showed that the same structures as well as a part of the left spinothalamic tract were affected.

In a section through the fourth ventricle it was seen that the area of softening had destroyed the lobulus simplex, lobulus ansiformis crus 1 and lobulus floccularis. The left lateral part of the lobulus C_2 vermalis was also implicated. There was, in addition, destruction of the dentate, emboliform and globose nuclei as well as of a part of the brachium pontis and brachium conjunctivum (fig. 3*B*). The greater part of the left brachium conjunctivum was shrunken (fig. 3*B*). In a section of the cerebellum and pons through the nuclei of the sixth and seventh nerves there was partial demyelinization of the brachium pontis, fibrae semicirculares internae and corpus restiforme. In a section of the medulla oblongata the right inferior olivary nucleus was atrophied and pale.

A section through the midbrain disclosed paling of the body of the right red nucleus and of its capsular fibers as a result of secondary degeneration (fig. 3*C*).

The left brachium conjunctivum was completely demyelinated. There was evidence of a recent hemorrhage along the border of the lateral part of the left red nucleus.

Comment.—Clinically, we were dealing with a syndrome of closure of the left superior cerebellar artery as revealed by "cerebellar signs" on the left side and sensory disturbances of spinothalamic origin on the right side. The signs of involvement of the pyramidal tract on the right were caused by the massive terminal hemorrhage which destroyed the internal capsule (fig. 3*A*). The complete obstruction of the left superior cerebellar artery caused the destruction of the lobulus anterior, lobulus simplex, lobulus ansiformis crus 1 and lobulus flocculoris (fig. 3*A* and *B*). As in case 1, the lateral parts of the lobulus II vermalis and lobulus IV vermalis were slightly implicated. The left cerebellar nuclei, brachium pontis and spinothalamic tract were also affected. In contrast to the changes in case 1 the brachium conjunctivum and lateral lemniscus were not as extensively involved. This was probably due to the collateral circulation. The slight involvement of the third nerve in this case was due not to disease of the superior cerebellar artery but to the lesion of the posterior cerebral artery.

CASE 3.—*Bilateral thrombosis of the mesial branches of the superior cerebellar arteries supplying the vermis and the mesial parts of the lobulus anterior, lobulus simplex and lobulus ansiformis crus 1. Signs of cerebellar involvement masked by the subacute combined degeneration.*

History.—M. S., a man aged 63, was admitted to the Montefiore Hospital on Sept. 17, 1931. He had been suffering from attacks of dizziness, headache and vomiting and from an attack of unconsciousness lasting two days. The condition improved, but three years later the patient became weak and anemic; after the latter symptoms appeared a diagnosis of pernicious anemia was made.

Neurologic Examination.—There were bilateral signs of involvement of the pyramidal tract and sensory disturbances referable to the posterior columns. There were, in addition, ataxia in both upper extremities, pseudo-athetotic movements of the fingers, stuttering, dysphagia and disturbances of memory.

Laboratory Data.—The blood picture was typical of that found in pernicious anemia; gastric analysis showed absence of free hydrochloric acid. All other data were normal.

Clinical and Anatomic Diagnosis.—The diagnosis was pernicious anemia, subacute combined degeneration and thrombosis of the mesial branches of the superior cerebellar artery.

Autopsy.—Gross Examination: There was marked atherosclerosis of the vessels at the base of the brain, especially the superior cerebellar arteries. The brain stem appeared shrunken. There was softening of the mesial parts of the cerebellum mainly implicating the vermis. The spinal cord was atrophic.

Microscopic Examination: In a horizontal section of the cerebellum and midbrain through the peduncles there was partial bilateral destruction of the lobulus II vermalis and lobulus IV vermalis and the mesial parts of the lobulus anterior, lobulus simplex and lobulus ansiformis crus 1 (fig. 4*A*). The right brachium conjunctivum was atrophied. There was also slight destruction of both dentate

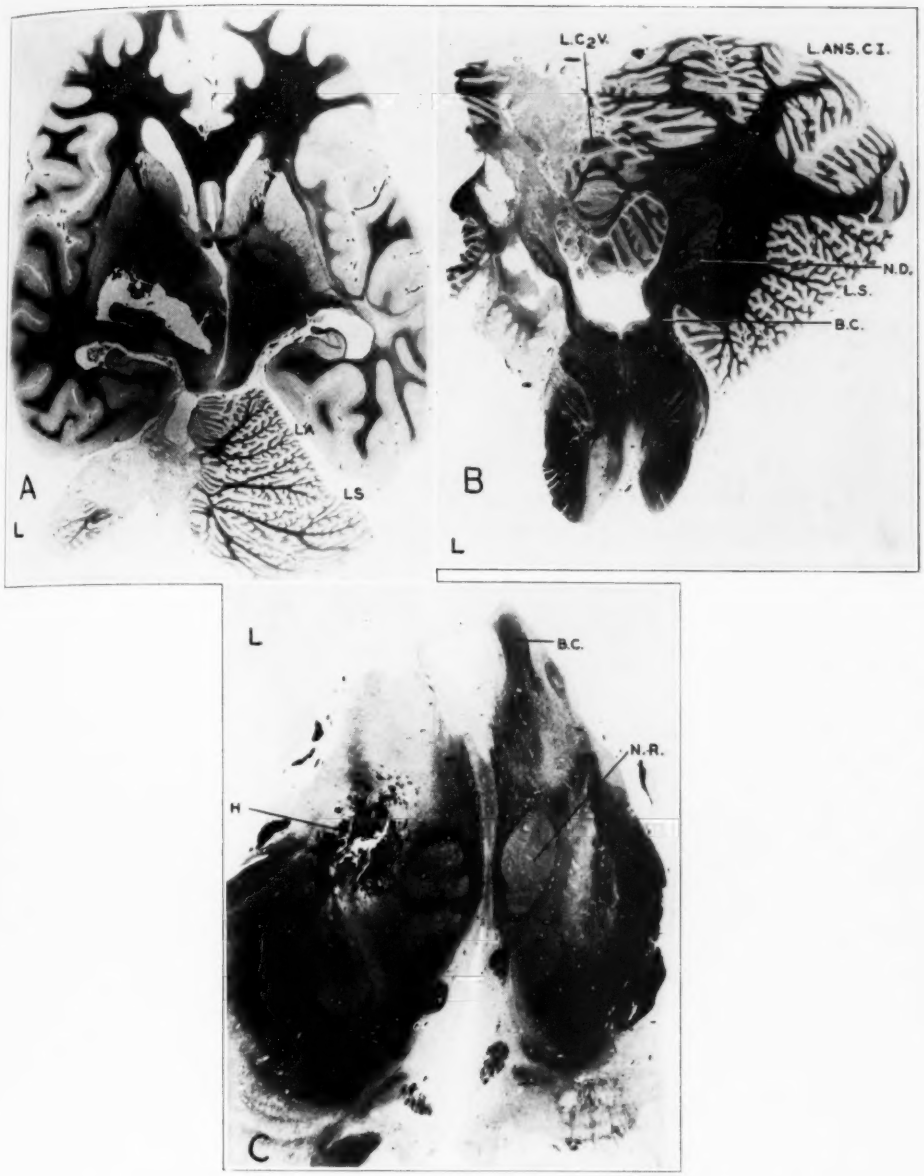

Fig. 3 (case 2).—*A*, horizontal section of the cerebrum and cerebellum, showing a hemorrhagic area in the distribution of the middle and posterior cerebral arteries. There is destruction of the cerebellum in the distribution of the left superior cerebellar artery with implication of the lobulus anterior (*L.A*), the lobulus simplex (*L.S*) and part of the lobulus ansiformis crus 1. Note that the lateral part of the vermis is only slightly involved. *B*, horizontal section of the cerebellum and pons through the fourth ventricle, showing destruction of the left lobulus simplex (*L.S*) and lobulus ansiformis crus 1 (*L.Ans.C.I.*), the left dentate nucleus (*N.D.*) and the other cerebellar nuclei and the left brachium conjunctivum and brachium pontis. The left lateral part of the lobulus C_2 vermalis (*L.C*$_2$*V.*) is slightly affected. *C*, horizontal section through the red nuclei. Notice the paling of the body of the right red nucleus (*N.R.*) and the poverty in its capsular fibers (compare with the corresponding structure on the left side). The left brachium conjunctivum (*B.C.*) is almost completely destroyed. The hemorrhagic area (*H*) on the left side is along the distribution of the posterior cerebral artery. Myelin sheath stain.

nuclei. In a section of the cerebellum and pons through the nuclei of the sixth and seventh nerves there was bilateral destruction of the lobulus C_2 vermalis and of the mesial parts of the lobulus ansiformis crus 1 (fig. 4 *B*). The process in the vermis was more extensive than that in the lateral lobes. The lobulus ansiformis crus 2 was spared. Sections through the red nucleus and inferior olives showed nothing noteworthy. The mesial branches of the superior cerebellar artery at their point of origin showed marked thickening of the intima, splitting of the lamina elastica and narrowing of the lumen. The changes in the spinal cord were typical of subacute combined degeneration such as is seen in pernicious anemia.

Comment—Objective signs of cerebellar involvement were not elicited in this case. As the type of ataxia was not described in detail we did not wish to attribute it to the lesion in the cerebellum, as it might be ascribed to lesions of the posterior columns due to the subacute combined degeneration. The attacks of dizziness, headache and vomiting which

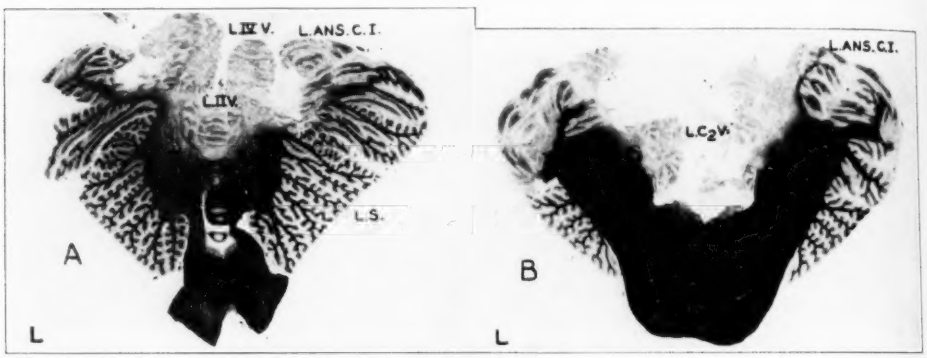

Fig. 4 (case 3).—*A*, horizontal section through the upper part of the fourth ventricle, showing bilateral destruction of the lobulus II vermalis (*L.II V.*) and lobulus IV vermalis (*L.IV V.*) and of the mesial parts of the lobulus anterior, lobulus simplex (*L.S.*) and lobulus ansiformis crus 1 (*L.Ans.C.I.*) as a result of endarteritis of the mesial branches of the superior cerebellar artery. The right brachium conjunctivum is atrophied. *B*, horizontal section through the nuclei of the sixth and seventh nerves, showing bilateral destruction of the lobulus C_2 vermalis (*L.C₂V.*) and mesial parts of the lobulus ansiformis crus 1 (*L.Ans.C.I.*). Myelin sheath stain.

occurred three years before the appearance of the pernicious anemia may possibly have been due to the cerebellar lesion. Unique in this case, in contrast to most of the other cases, is the involvement of the mesial branches of the superior cerebellar artery with destruction of the lobulus II vermalis, lobulus IV vermalis, and lobulus C_2 vermalis and the mesial parts of the lobulus anterior, lobulus simplex and lobulus ansiformis crus 1. The lobulus ansiformis crus 2 is completely spared in cases of thrombosis of the mesial branches of the superior cerebellar artery.

CASE 4.—*Incomplete occlusion of both superior cerebellar arteries. Bilateral signs of cerebellar involvement, dysarthria and impaired sensation to pain and cold on the left side. Partial involvement of the lobulus anterior, lobulus simplex and lobulus ansiformis crus 1 bilaterally, of the brachium conjunctivum, more pronounced on the left side than on the right, of the brachium pontis bilaterally, of the lateral part of the right medial lemniscus, and of the dentate nucleus and the other cerebellar nuclei bilaterally.*

History.—H. U., a man aged 65, was admitted to the hospital on March 14, 1930. In August 1929 there developed loss of speech and paralysis on the left side. After some improvement had taken place another cerebral accident occurred in February 1930.

Neurologic Examination.—Cerebellar ataxia, a bilateral Gordon Holmes sign and dysdiadokokinesia were noted. There were coarse tremors of the head when the patient was in the sitting position and tremors of the lower jaw. Speech was dysarthric, explosive and slow. The deep reflexes on the right were slightly hyperactive, but there were no signs of involvement of the pyramidal tract; the deep reflexes on the left were diminished. The fundi showed marked arteriosclerotic changes. There was a supranuclear weakness on the left side of the face. Perception of pain and cold was impaired on the left side, but all other forms of sensation were preserved. The systolic blood pressure was 150, and the diastolic pressure, 70.

Clinical and Anatomic Diagnosis.—The diagnosis was cerebellar arteriosclerosis, occlusion of the coronary arteries, generalized arteriosclerosis.

Laboratory Data.—The tests gave negative results.

Course.—On Oct. 16, 1931, there developed occlusion of the coronary artery. The results of the neurologic examination remained unchanged. A lumbar puncture on that day disclosed a clear fluid without pleocytosis. The patient died about fifteen minutes after the signs of coronary occlusion had appeared.

Autopsy.—Gross Examination: The frontal convolutions were atrophic. The internal carotid, basilar and vertebral arteries were the seat of atherosclerotic plaques. The left vertebral was about four times the size of the right vertebral artery. The brain was cut horizontally. There was an area of softening along the course of the right posterior cerebral artery with destruction of the fusiform, lingual and part of the occipital convolutions. There were also softenings of both cerebellar lobes and distortion of the fourth ventricle.

Microscopic Examination: A section through the aqueduct disclosed partial softening of some of the right cerebellar convolutions belonging to the lobulus anterior. The brachium conjunctivum was diminished in size bilaterally and stained poorly, the right brachium being more affected than the left. The right lateral part of the medial lemniscus was slightly demyelinated. A section through the fourth ventricle revealed softening of part of the right lobulus anterior and of the lobulus simplex bilaterally, but more on the right than on the left side (fig. 5*A*). The brachium conjunctivum, the lateral lemniscus, the descending root of the fifth nerve and the lateral parts of the medial lemnisci were diminished in size and stained poorly (fig. 5*A*). The vermis was intact. A section of the cerebellum and pons through the nucleus of the sixth nerve disclosed softening of part of the lobulus simplex, lobulus ansiformis crus 1 and lobulus floccularis and the dentate, emboliform and globose nuclei on both sides, the left side showing more softening than the right (fig. 5*B*). The left lobulus floccularis stained poorly. There was bilateral shrinkage of the brachium conjunctivum (fig. 5*B*). There was demyelinization of the brachium pontis on both sides and of the fibers

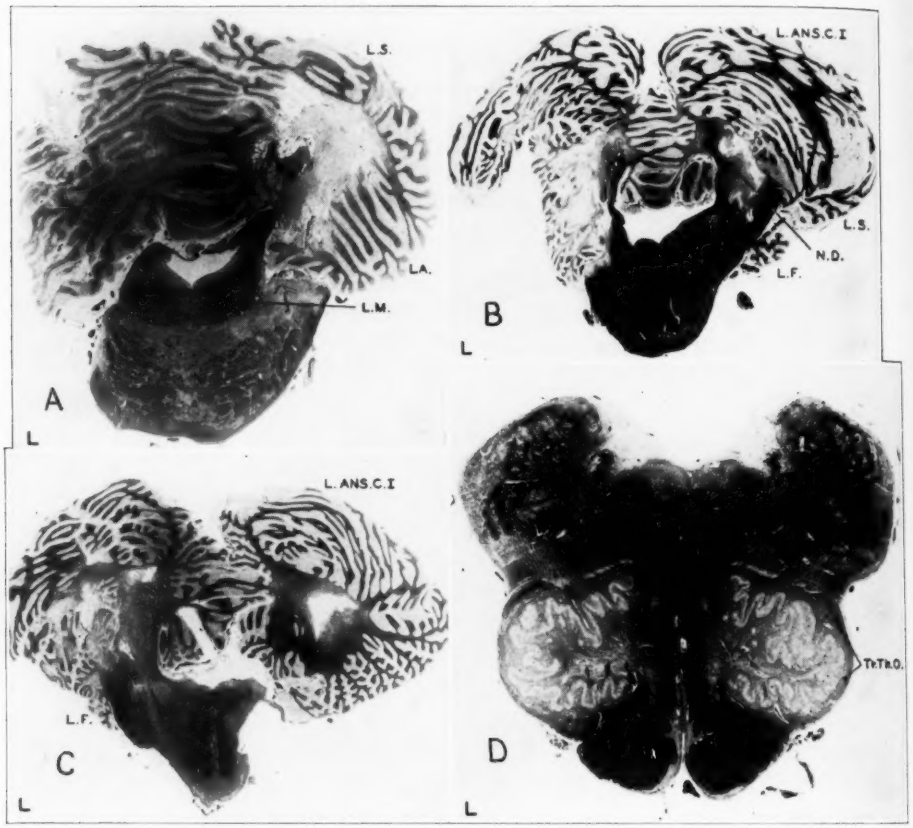

Fig. 5 (case 4).—*A*, horizontal section through the fourth ventricle. Incomplete occlusion of both superior cerebellar arteries, more marked on the right than on the left. Notice the softening of the right cerebellar convolutions belonging to the lobulus anterior (*L.A.*), the lobulus simplex (*L.S.*) and the lesser involvement of the same structures on the left. The brachium conjunctivum was diminished in size bilaterally. The lateral parts of the medial lemniscus (*L.M.*) stained poorly. *B*, horizontal section of the cerebellum and pons passing through the nucleus of the sixth nerve and disclosing softening of the cerebellar convolution belonging to the lobulus simplex (*L.S.*) and the lobulus ansiformis crus 1 (*L. Ans. C.I.*) bilaterally, more marked on the left than on the right, as well as the left lobulus floccularis (*L.F.*) and the dentate nuclei (*N.D.*). The brachium conjunctivum was markedly shrunken bilaterally. *C*, horizontal section of the cerebellum and medulla oblongata through the nucleus of the eighth nerve, disclosing lesions similar to those shown in figure 5 *B*. Notice the cysts replacing the white matter of the cerebellum. *D*, section of the medulla oblongata, disclosing hypertrophy and paling of both inferior olives. Notice the paling of the tractus thalamo-olivaris (*Tr.Th.O.*) bilaterally. Myelin sheath stain.

of the facial nerve on the right side. A section through the cerebellum and the medulla oblongata at about the level of the nuclei of the eighth and ninth nerves showed that part of the same cerebellar lobes were involved as in the previous section, the left side being more affected than the right (fig. 5 *C*). A cyst replaced part of the destroyed white matter of the right hemisphere of the cerebellum (fig. 5 *C*). At this level there was also partial involvement of the right corpus restiforme (fig. 5 *C*). Sections of the medulla oblongata in the region of the inferior olive disclosed bilateral hypertrophy and paling of the olives and bilateral shrinkage and paling of the tractus thalamo-olivaris (fig. 5 *D*). A section through the red nuclei showed bilateral paling of the red nuclei and their capsular fibers, more pronounced on the right than on the left.

Comment.—This case is of particular interest because of the incomplete and bilateral involvement of the superior cerebellar artery and the implication of the corpus restiforme.

CASE 5.—*Bilateral incomplete obstruction of branches of the superior cerebellar arteries, more pronounced on the left than on the right; the "cerebellar signs" and the sensory disturbances elicited were unsatisfactory because of the massive cerebral lesions. Involvement of the dentate nucleus and white matter of the cerebellum on the right side and of the dentate, emboliform and globose nuclei, white matter of the cerebellum, lobulus ansiformis crus 1, lobulus flocculoris, lobulus ansiformis crus 2 (slight), brachium conjunctivum and corpus restiforme on the left.*

History.—P. S., a woman aged 63, was admitted to the Montefiore Hospital on Oct. 1, 1930. There was a history of hypertension of seven years' duration. The patient was well until 1929, when she became easily fatigued and had attacks of vomiting two or three times a day, the disorder lasting for three days with an interval of relief for one or two days. In September 1930 there developed paralysis of the right side of the body.

General Examination.—There was a systolic murmur over the apex and aorta, and the aortic second sound was accentuated. The systolic blood pressure was 240, and the diastolic pressure, 155.

Neurologic Examination.—The patient was bedridden. Coordination tests gave unsatisfactory results because of the mental state. There was forced grasping in both hands. All the extremities were paretic. On both sides there were exaggeration of the reflexes, a Babinski sign and allied responses. Sensation could not be tested satisfactorily because of the patient's mental state; when the temperature sensation was being tested the patient said "cold" when either hot or cold was applied to the body, and no positive inference could be drawn. The fundi showed marked retinal sclerosis, and there was exudate in both eyes. There were marked mental changes, intellectual enfeeblement—the patient talked irrelevantly and incoherently—loss of insight, change in personality and periods of restlessness. The patient passed into stupor and died on Oct. 17, 1930.

Laboratory Data.—The urea nitrogen content was 25.3 mg. per hundred cubic centimeters. The urine contained hyaline casts.

Clinical and Anatomic Diagnosis.—The diagnosis was generalized cerebral and cerebellar arteriosclerosis and chronic nephritis.

Autopsy.—Gross Examination: All the cerebral vessels disclosed marked atherosclerotic changes. The brain was cut horizontally. There was softening of both cerebral hemispheres along the course of distribution of the middle cerebral arteries. There was also evidence of a more recent hemorrhage in the left brachium conjunctivum, corpus restiforme and dentate nucleus, and an area of softening

involved part of the white matter of the right hemisphere of the cerebellum and right dentate nucleus.

Microscopic Examination.—In a section of the pons through the fourth ventricle, the left brachium conjunctivum and part of the descending root of the fifth nerve were replaced by a hemorrhagic area (fig. 6 *A*). In a section through the pons in the region of the nuclei of the sixth and seventh nerves, the hemorrhage had destroyed on the left side the dentate, emboliform and globose nuclei, the brachium conjunctivum and parts of the corpus restiforme and brachium pontis (fig. 6 *B*). In a section through the cerebellum and medulla oblongata there were two areas

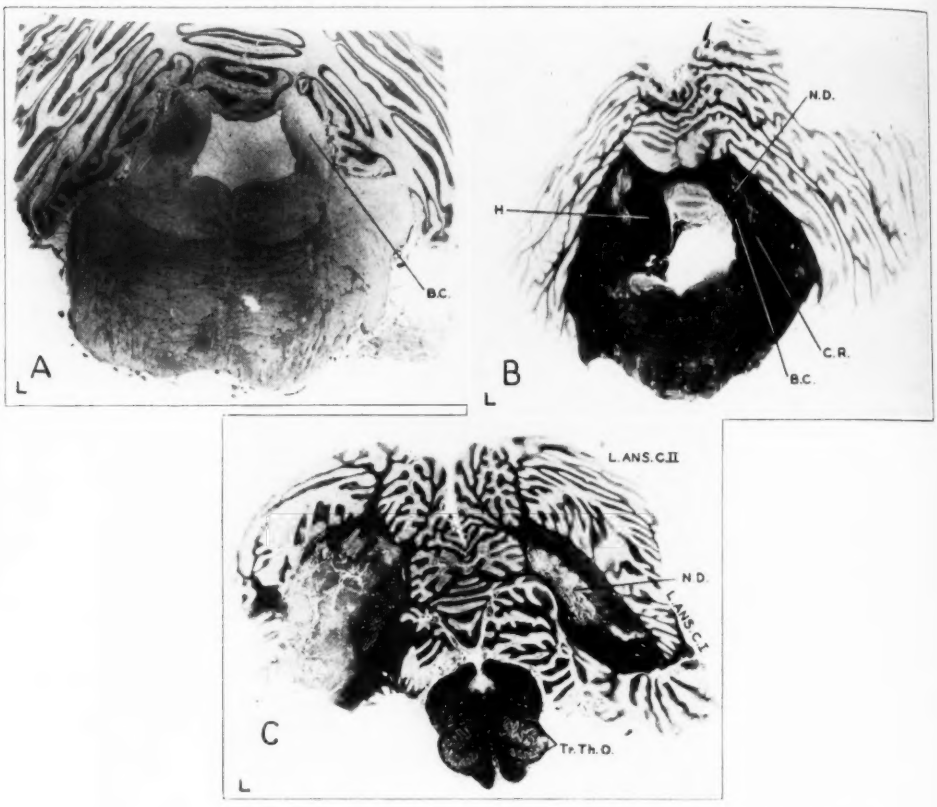

Fig. 6 (case 5).—*A*, horizontal section through the fourth ventricle, showing a hemorrhagic mass destroying the left brachium conjunctivum (*B.C.*) and part of the descending mesencephalic root of the fifth nerve; cresyl violet stain. *B*, a hemorrhagic area (*H*) with destruction of the left dentate nucleus (*N.D.*), emboliform and globose nuclei and brachium conjunctivum (*B.C.*) and part of the left corpus restiforme (*C.R.*). *C*, horizontal section of the cerebellum and the medulla oblongata. On the right there is destruction of the dentate nucleus (*N.D.*) and white matter of the cerebellum; on the left, part of the dentate nucleus, lobulus ansiformis crus 1 (*L.Ans.C.I.*) and lobulus ansiformis crus 2 (*L.Ans. C.II*) are involved. Notice the paling of the right inferior olive and thalamo-olivary fibers (*Tr. Th.O.*). Myelin sheath stain.

of softening implicating part of the right dentate nucleus and the white matter of the right hemisphere of the cerebellum. On the left side there was destruction of the white matter of the cerebellum, part of the dentate nucleus and the lobulus ansiformis crus 1 and lobulus floccularis; some of the folia of the lobulus ansiformis crus 2 were also involved (fig. 6*C*). The branch of the superior cerebellar artery supplying these structures disclosed marked thickening of the intima and breaking down of the lamina elastica. With higher magnification some changes could be demonstrated in the cortical convolutions of the cerebellum belonging to the lobulus simplex. Disintegration of the myelin sheaths and liquefaction necrosis were noted in the white matter. The inner cerebellar arteries were thickened, and some of their lumens were obliterated by organized thrombi. The nerve cells of the right dentate nucleus stained poorly and showed pigment atrophy. The right inferior olive of the medulla oblongata was paler than the left (fig. 6*C*), and the thalamo-olivary fibers stained poorly. A section through the midbrain disclosed paling of the right red nucleus and of its capsular fibers. In a section through the decussation of the brachia conjunctiva, the left brachium was demyelinated.

The cervical region of the spinal cord showed descending demyelinization of both crossed pyramidal tracts.

Comment.—Owing to the mental state of the patient it was impossible to make a satisfactory sensory examination. The massive bilateral cerebral involvement masked the signs of cerebellar disease. The implication of the corpus restiforme is worthy of mention.

CASE 6.—*Incomplete obstruction of a branch of the right superior cerebellar artery; signs of cerebellar involvement on the right side and sensory disturbances on the left side. Destruction of the brachium conjunctivum, the corpus restiforme, the descending root of the fifth nerve, the nuclei of the sixth and seventh nerves, the posterior longitudinal bundle, part of the brachium pontis and the medial lemniscus and slight involvement of the lobulus simplex on the right side.*

History.—A. B., a woman aged 51, was admitted to the hospital on Dec. 8, 1930. In July 1930 she had had attacks of severe headache and dizziness. This was followed by difficulty in speaking and in chewing and weakness in the right arm and leg.

General Examination.—There were marked carotid pulsations, a soft systolic murmur at the apex, transmitted over the precordium, and enlargement of the heart to the left. The systolic blood pressure was 160, and the diastolic, 80.

Neurologic Examination.—There were coarse tremor of the right hand, clonic movements of the jaw, slurring in speech and slight dysarthria. The right upper extremity was hypotonic. There was a Gordon Holmes phenomenon on the right and adiadokokinesis of the right upper extremity. Horizontal and rotatory nystagmus occurred in all directions. Motor power was diminished in the right upper and lower extremities. All the deep reflexes were increased on the right. There were a Babinski sign and allied responses on the right. The abdominal reflexes were present. There were hypesthesia, hypalgesia and hypothermesthesia over the left side of the body, including the face. The sense of position and vibration, stereognosis and two point discrimination were normal. There were hypalgesia and hypothermesthesia over all divisions of the left fifth nerve, including the mucous membranes. There was no corneal hypesthesia. The jaw deviated to the right, and the jaw reflexes were increased bilaterally. There was no apparent diminution of power or atrophy of the masseter, temporal or pterygoid muscles on the

right. There was slight internal strabismus of the left eye; extreme lateral gaze to the left could be maintained for several seconds only and then the eyes deviated back to the midline. There was apparently a defect in associated movements to the left. The pupils were equal and reacted to all stimuli. The right palpebral fissure was smaller than the left. There was slight peripheral weakness of the right side of the face. The palate moved poorly but equally on the two sides. The tongue deviated to the right. Speech was almost unintelligible and of a nasal quality.

Laboratory Data.—There was a complete block of the spinal fluid with a Froin syndrome; the total protein content of the fluid was from 114.4 to 154 mg. per hundred cubic centimeters. The Wassermann reaction of the blood was 4+ on two occasions. The Wassermann reaction of the spinal fluid was negative. The spinal fluid contained 90 cells, all lymphocytes. Injection of iodized poppy-seed oil 40 per cent showed that the oil permeated the cervical region as far as the fifth dorsal vertebra, where there appeared to be a complete block to further passage of the opaque material.

Course.—The patient received antisyphilitic treatment; she died on Jan. 16, 1931, of bronchopneumonia.

Clinical and Anatomic Diagnosis.—The diagnosis was cerebrovascular syphilis.

Autopsy.—Gross Examination: There was incomplete occlusion of the left middle cerebral artery, with softening along the distribution of the caudate nucleus, putamen and internal capsule. Another area of softening had destroyed the brachium conjunctivum and part of the cerebellum, corpus restiforme and brachium pontis on the right side. This area ascended into the pons for a distance of about 0.5 cm. The cord was softened in the third thoracic segment, and the dura was thickened.

Microscopic Examination: In a coronal section through the region of the brachium conjunctivum and cerebellum on the right side there was an area of destruction involving the anterior medullary velum, brachium conjunctivum, lateral lemniscus and descending root of the fifth nerve, part of the nuclei of the sixth and seventh nerves, the posterior longitudinal bundle, part of the brachium pontis and part of the lobulus simplex of the cerebellum (fig. 7 *A*). The lateral part of the right medial lemniscus was also involved; this was best seen in sections at higher levels. The left pyramid was somewhat shrunken and slightly paler than the right, owing to descending demyelinization. The intima of the vessels in these regions was markedly thickened, and the lumens were narrow; the vessels showed the appearance typical of Heubner's endarteritis syphilitica. In sections of the medulla oblongata and cerebellum through the nuclei of the ninth and tenth nerves there was on the right side implication of the brachium conjunctivum, part of the brachium pontis, the anterior medullary velum, part of the cerebellum, the corpus restiforme and the nucleus radix spinalis trigemini. The left inferior olive was slightly hypertrophied and paler than the right (fig. 7 *B*). In a section through the decussation of the brachia conjunctiva, almost at the beginning of the decussation, there was paling of the fibers on the left side, an evidence of ascending degeneration. A section through the red nuclei and the third ventricle disclosed paling of the left red nucleus and its capsular fibers (fig. 7 *C*) as a result of the ascending degeneration of the superior cerebellar peduncle. There was also demyelinization of the left cerebral peduncle.

Comment.—The signs of cerebellar involvement on the right side and the sensory disturbances on the left were due to syphilitic disease of a branch of the right superior cerebellar artery. This branch also

supplied the descending mesencephalic root of the fifth nerve, part of the nuclei of the sixth and seventh nerves, the posterior longitudinal bundle, part of the brachium pontis, the corpus restiforme and the anterior medullary velum. The two other lesions in the internal capsule and the one in the spinal cord interfered little with the clinical picture resulting from disease of the branch of the superior cerebellar artery. The cerebellum, except for a small part of the lobulus simplex adjacent to the brachium conjunctivum, was intact. The lateral part of the medial lemniscus (spinothalamic tract) was definitely implicated. The

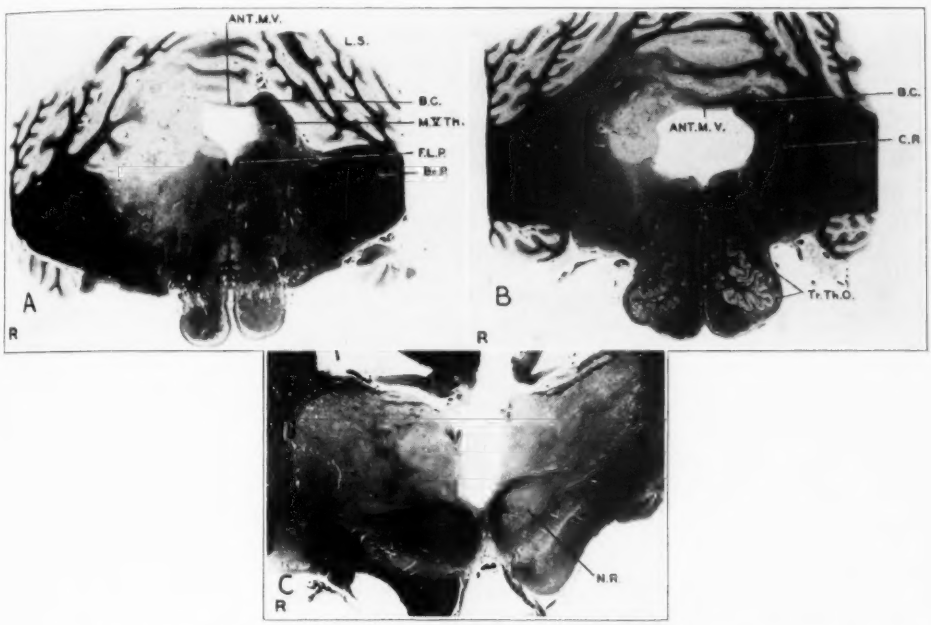

Fig. 7 (case 6).—*A*, coronal section of the medulla oblongata, showing an area of destruction on the right side in the region of the fifth brachium conjunctivum (*B.C.*), descending mesencephalic root of the fifth nerve, (*M.V.Th.*), nucleus of the sixth nerve and posterior longitudinal bundle (*F.L.P.*), part of the brachium pontis (*Br.P.*) and the inner part of the lobulus simplex (*L.S.*). *B*, coronal section of the medulla oblongata through the nuclei of the ninth and tenth nerves with destruction of the right brachium conjunctivum (*B.C.*) corpus restiforme (*C.R*), anterior medullary velum (*Ant.M.V.*) and descending root of the fifth nerve. Notice the hypertrophy and paling of the left inferior olive and the paling of the tractus thalamo-olivaris (*Tr.Th.O.*). *C*, coronal section through the posterior part of the third ventricle. Notice the paling of the left red nucleus (*N.R.*) and the poverty in its capsular fibers as a result of destruction of the right brachium conjunctivum. The demyelinization of the left peduncle is the result of a descending degeneration. Myelin sheath stain.

paralysis of the sixth nerve was accounted for by the involvement of its nucleus. The difficulty in conjugate movements of the eye was probably a result of implication of the parabducens nucleus.

CASE 7.—*Bilateral rupture of branches of the superior cerebellar arteries. Palsy of the left sixth and seventh nerves. Signs of cerebellar involvement and sensory disturbances not elicited owing to unconsciousness. Bilateral destruction of the brachium conjunctivum, medial and lateral lemnisci, corpus restiforme, more pronounced on the right than on the left, nucleus of the sixth nerve and genu of the seventh nerve. Slight implication of part of the right lobulus anterior.*

History.—S. L., a woman aged 38, was admitted to the Montefiore Hospital on Nov. 25, 1919. The history was that right hemiplegia had appeared suddenly in 1918 and disappeared completely in one month. Six months later there occurred a second stroke and aphasia. The aphasia disappeared in three weeks.

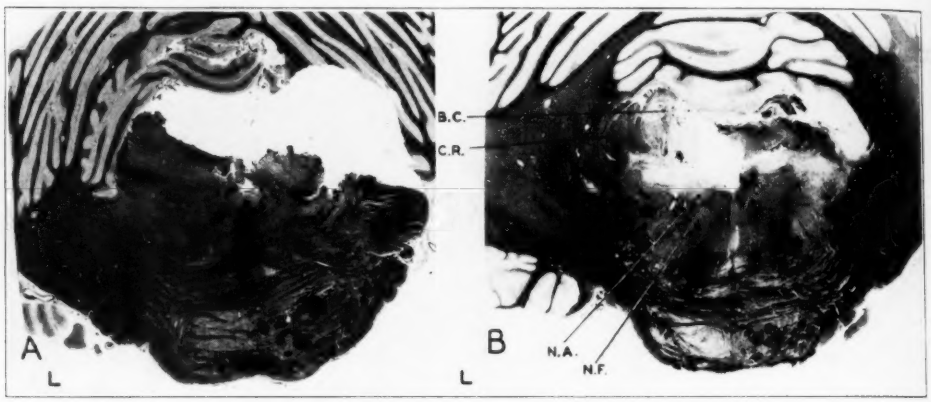

Fig. 8 (case 7).—*A*, section through the tegmentum and pons, showing destruction of part of the hemisphere of the cerebellum, the brachium conjunctivum and brachium pontis, the descending root of the fifth nerve, the tractus thalamo-olivaris and part of the medial lemniscus on the right side. The same structures on the left were involved to a lesser degree. Part of the left pyramid showed an area of descending demyelinization. *B*, section through the nuclei of the sixth nerves, in which the lesion was more extensive in the region of the brachium conjunctivum (*B.C.*) and corpus restiforme (*C.R.*). The right side was more involved than the left. Notice the implication of the nucleus of the sixth nerve (*N.A.*) and of the genu of the seventh nerve (*N.F.*), especially on the right side. Myelin sheath stain.

General Examination.—There were enlargement of the heart to the left and an accentuation of the aortic second sound; the systolic blood pressure was 152, and the diastolic pressure, 104.

Neurologic Examination.—There were: spastic paralysis of the right upper and lower extremities, exaggeration of the deep reflexes and a Babinski sign on the right side and partial motor aphasia. Hypalgesia and diminished vibratory and deep muscular sensibility were noted on the right side of the body. The pupils were equal and regular and reacted to all stimuli.

Laboratory Data.—The Wassermann reaction of the blood was positive on one occasion. The Wassermann reaction of the cerebrospinal fluid was negative. There was a faint trace of albumin in the urine, and the result of the concentration test was 1.030.

Course.—The patient received antisyphilitic treatment until the serologic test was negative. The hemiplegia and aphasia improved somewhat. On Oct. 1, 1930, she suddenly lost consciousness. The pupils were unequal but reacted to all stimuli. The right hemiplegia increased. There were paralysis of the right external rectus muscle and slight peripheral facial weakness on the right side. Sensation and signs referable to the cerebellum could not be tested, as the patient was unconscious. The blood pressure was 210 systolic and 90 diastolic. A spinal tap made at this time elicited bloody fluid. The patient died within twenty hours after the vascular insult.

Autopsy.—Gross Examination: The basilar and right vertebral arteries were the seat of atheromatous plaques. The brain was cut coronally. There was evidence of an old hemorrhage in the region of the left middle cerebral artery. A recent hemorrhage had destroyed part of the right brachium conjunctivum, corpus restiforme, and medial and lateral lemnisci in the pons. Some of the cerebellar fibers were also implicated.

Microscopic Examination: Sections through the brachium pontis, the brachium conjunctivum and the nucleus of the fifth nerve on the right side disclosed partial destruction of the anterior medullary velum, lobulus anterior and medial lemniscus. The brachium conjunctivum, brachium pontis, descending root of the fifth nerve, tractus thalamo-olivaris and lateral lemniscus were more extensively involved (fig. 8*A*). The same structures were implicated to a less degree on the left side (fig. 8*A*). Part of the left pyramid showed descending demyelinization. The vessels of the pons showed marked atherosclerotic changes. The pathologic process described for this section extended as far down as the nucleus of the sixth nerve. At that level the lesion was more extensive in the region of the brachium conjunctivum and corpus restiforme (fig. 8*B*). The nucleus of the sixth and the genu of the seventh nerve were also implicated, slightly more on the right. There was a slight hemorrhagic area in the genu of the seventh nerve (fig. 8*B*). A small part of the lobulus simplex at this level was destroyed. In a section through the medulla oblongata the inferior olivary nuclei were pale, the left nucleus more than the right.

Comment.—The syndrome of the brachium conjunctivum could not be demonstrated, as the hemorrhage in this area occurred twenty hours before death.

CASE 8.—*Rupture of a branch of the right superior cerebellar artery supplying the brachium conjunctivum, lateral lemniscus, descending root of the fifth nerve and lateral part of the medial lemniscus. Signs of cerebellar involvement and sensory disturbances not elicited, as the hemorrhage was terminal.*

History.—S. F., a man aged 43, was admitted to the Montefiore Hospital on Jan. 13, 1933. He had suffered from headaches and hypertension for fifteen years. In March 1932 he had had an attack of vomiting, shortness of breath and choking sensation, followed by disturbance in gait and aphasia.

General Examination.—At the time of admission there were hypertension, the pressure being 250 systolic and 150 diastolic, and evidence of cardiac hypertrophy.

Neurologic Examination.—Slow and shuffling gait, hemiparesis and increase of the deep reflexes on the right side and aphasia were noted.

Laboratory Data.—The fixed urinary concentration test showed that the specific gravity was from 1.010 to 1.014. The urine contained a large amount of albumin and numerous casts.

Course.—Two days after admission the patient complained of severe frontal headache; the appearance of the headache was followed immediately by convulsive movements. He sank into coma and ceased to breathe shortly thereafter. Examination during the convulsive movements disclosed: stertorous breathing, bilateral edema of the optic disks with evidence of hemorrhages, dilatation and fixation of the pupils, hyperactive reflexes on the right, diminished reflexes on the left and a Hoffmann sign on both sides.

Clinical and Anatomic Diagnosis.—The diagnosis was: intraventricular cerebral hemorrhage, thrombosis of the left middle cerebral artery, rupture of the branch of the right superior cerebellar artery and malignant hypertension.

Autopsy.—Gross Examination: The arteries at the base of the brain contained atheromatous plaques. There were complete thrombosis of the left middle cerebral

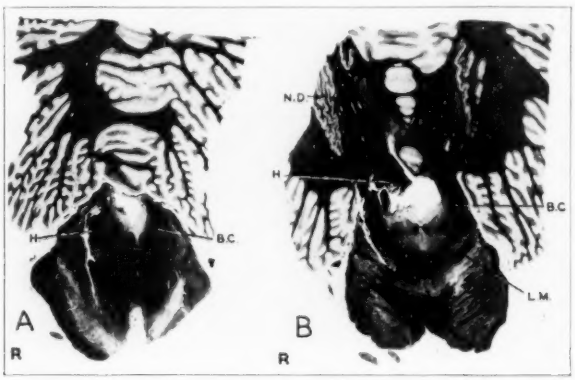

Fig. 9 (case 8).—*A*, hemorrhagic area (*H*) with destruction of the fibers of the right brachium conjunctivum (*B.C.*) and lateral lemniscus and part of the medial lemniscus, the descending mesencephalic root of the fifth nerve and the locus caeruleus. *B*, section showing a hemorrhagic area (*H*) in the right brachium conjunctivum (*B.C.*) and involvement of the lateral part of the right medial lemniscus (*L.M.*). Myelin sheath stain.

artery and softening of the structures supplied by this vessel. Evidence of small recent hemorrhages was present in the region of the right thalamus and pulvinar. A small hemorrhagic area was also present in the midbrain; it had destroyed the right brachium conjunctivum and lateral lemniscus (fig. 9*A*). The cerebellum was intact.

Microscopic Examination: A section through the pes pedunculi and cerebellum revealed evidence of a small hemorrhage on the right side which had destroyed the brachium conjunctivum, the lateral lemniscus, part of the locus caeruleus and the descending mesencephalic root of the fifth nerve (fig. 9*A*). In a section through the cerebellum and pons in the region of the fourth ventricle it was seen that the hemorrhage had destroyed part of the right brachium conjunctivum as it emerged from the dentate nucleus, the right lateral lemniscus and the lateral part of the right medial lemniscus (fig. 9*B*). A section at a higher level, in the

region of the midbrain, disclosed paling of the left red nucleus and poverty in its capsular fibers. In a section through the medulla oblongata the left inferior olive appeared hypertrophied and pale. There was a tear in the branch of the right superior cerebellar artery.

Comment.—In this case the clinical diagnosis of a lesion disclosing a syndrome referable to the brachium conjunctivum could not be made, as the hemorrhage was terminal.

CASE 9.—*Thrombosis of the dentate branch of the right superior cerebellar artery supplying the dentate nucleus; signs of cerebellar involvement on the right side. Destruction of the dentate and other cerebellar nuclei and part of the brachium conjunctivum on the right side.*

History.—P. D., a man aged 62, was admitted to the Montefiore Hospital on July 31, 1928. He had had hypertension for eight years. In May 1928 he became dizzy and fell.

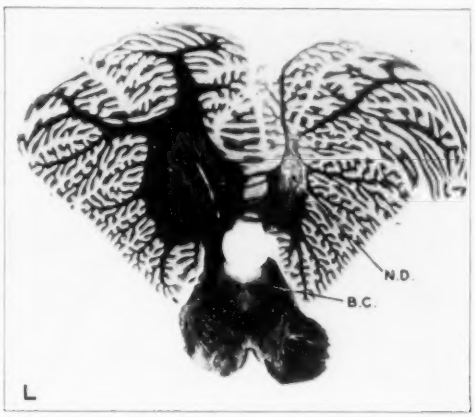

Fig. 10 (case 9).—Horizontal section of the cerebellum through the fourth ventricle, showing destruction of the right dentate nucleus (*N.D.*) and slight implication of the fibers of the brachium conjunctivum (*B.C.*). Myelin sheath stain.

General Examination.—The heart was enlarged to the left, and the blood pressure was 160 systolic and 110 diastolic.

Neurologic Examination.—The patient walked on a broad base and was slightly ataxic. The right upper extremity was hypotonic, and there was a Gordon Holmes phenomenon on the right side. The deep reflexes were slightly hyperactive. There were exudates in both retinas, and the retinal vessels were atherosclerotic. There was central facial weakness.

Laboratory Data.—Albumin was present in the urine, and the specific gravity varied between 1.015 and 1.018. The urea nitrogen content of the blood was 22.8 mg. per hundred cubic centimeters.

Course.—The patient's condition improved, and he was discharged on Oct. 19, 1928. He was well until February 1932, when a second vascular insult resulting in right hemiplegia and some aphasia developed. Neurologic examination at this time elicited signs of a right hemiplegia, slight dysarthria and tremor of the left hand.

Clinical and Anatomic Diagnosis.—The diagnosis was cerebral and cerebellar arteriosclerosis.

Autopsy.—Gross Examination: The cerebral vessels were atherosclerotic. The right vertebral artery was twice the size of the left. There were small areas of softening in the brain along the branches of the left middle cerebral artery. In addition there was an area of softening in the right dentate nucleus.

Microscopic Examination.—A horizontal section of the cerebellum and pons through the fourth ventricle disclosed destruction of the right dentate, globose and emboliform nuclei (fig. 10). The fibers of the right brachium conjunctivum were slightly implicated at the point at which they emerged from the dentate nucleus (fig. 10). There was also slight involvement of the adjacent lobulus simplex. The medial lemniscus was intact.

Comment.—The signs of cerebellar involvement, consisting of ataxia, hypotonia of the right upper extremity and the Gordon Holmes sign are readily explained by thrombosis of the branch of the right superior cerebellar artery supplying the dentate nucleus and the emerging fibers of the brachium conjunctivum. This was the only case in our group in which the dentate branch alone was implicated.

CLINICAL AND ANATOMIC CONSIDERATIONS

Complete obstruction of the superior cerebellar artery supposedly gives rise to the following symptoms: (1) homolateral signs of cerebellar involvement, (2) homolateral involuntary movements, especially of the upper extremity, and (3) contralateral sensory disturbances, generally dissociated and of the syringomyelic type. Not all of the cases recorded in the literature (Mills;[12] Guillain, Bertrand and Péron;[13] Worster-Draught and Allen;[14] Tchernysheff and Grigorowsky;[15] Russel,[16] and Critchley and Schuster[17]) conformed to the classic syndrome. In certain cases some of the symptoms were absent; in others there were additional manifestations. The most inconstant findings were the sensory disturbances and the involuntary movements. An analysis of our cases and a comparison with those recorded in the literature will help to clarify these problems.

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Signs and Symptoms of Cerebellar Involvement.—Signs and symptoms due to involvement of the cerebellar lobes or of the brachium conjunctivum were present in all our cases except cases 3, 7 and 8. In case 3 the ataxia present was not considered to be due to cerebellar disease because of the superimposition of subacute combined degeneration associated with pernicious anemia. In this disease, as is well known, the ataxia is due to degeneration of the posterior columns. The disease of the cerebellum in this case was limited to the vermal portion as a result of bilateral thrombosis of the medial branches of the superior cerebellar artery (figs. 4*A* and *B*). In cases 7 and 8 the signs referable to the cerebellum could not be elicited as the lesions developed just before death and the patients were unconscious. In this respect these two cases resemble the one described by Tchernysheff and Grigorowsky [15] and case 6 of Critchley and Schuster.[17] The symptoms of cerebellar involvement in our cases were disturbances in gait (walking on a broad base), ataxia, hypotonia, the Gordon Holmes phenomenon and intention tremor. Other disturbances, such as nystagmus, slow and drawling speech and areflexia, may also be considered as indicative of involvement of the cerebellum. These phenomena will be discussed later.

Involuntary Movements.—Such movements were noted only in cases 4, 6 and 9. They consisted of coarse tremor of the head and lower jaw in case 4, of coarse tremor of the right hand and clonic movements of the jaw in case 6 and of tremor of the left hand in case 9. It is to be emphasized that in case 9 the tremor was on the side opposite to that on which one would expect to find it, for the dentate nucleus and brachium conjunctivum were diseased on the right side. A similar observation was recorded by Critchley and Schuster [17] in their case 1. They explained the contralateral "cerebellar signs" on the basis that in some subjects there may be uncrossed fibers from the red nucleus to the spinal cord. The stimulus is thus diverted to the contralateral side instead of to the side of the lesion. Tremor was observed by Critchley and Schuster [17] in five of their six cases. Some observers consider the brachium conjunctivum and the dentate nucleus as the structures which control tremor. The fact that pathologic changes were present in these structures in eight of nine of our cases while tremor was present in only three makes it probable that there are other factors which account for this phenomenon. Twitching and undulating movements, such as those described by Guillain, Bertrand and Péron [13] and Worster-Draught and Allen,[14] were not observed in any of our cases.

In the first two cases, in which there was complete occlusion of the superior cerebellar artery, the clinical picture conformed to the classic syndrome described. These patients presented homolateral signs of cerebellar involvement and contralateral sensory disturbances.

Histopathologically, the following structures were found uniformly involved in cases 1 and 2: the brachium conjunctivum, part of the brachium pontis and corpus restiforme, the descending mesencephalic root of the fifth nerve, part of the medial lemniscus, the lobulus anterior, lobulus simplex, lobulus ansiformis crus 1 and lobulus floccularis and part of the cerebellar nuclei (dentate, globose and emboliform nuclei). The lobulus II vermalis, lobulus IV vermalis and lobulus C_2 vermalis, which are irrigated by the same vessel, were involved only slightly in their lateral portions. This is to be accounted for by the anastomosis with the opposite mesial branch of the superior cerebellar artery. The inner nuclei of the cerebellum (dentate, globose and emboliform nuclei) are supplied by a branch of the superior cerebellar artery and not by a branch of the posterior inferior cerebellar artery as maintained by Shellshear.[10] In case 3, in which both mesial branches of the superior cerebellar artery were thrombosed, the lobulus II vermalis, lobulus IV vermalis and lobulus C_2 vermalis were destroyed as well as the most medial parts of the lobulus anterior and lobulus simplex. The signs of cerebellar involvement in this case were masked by the picture of subacute combined degeneration.

In cases 4 and 5, in which there was incomplete occlusion of both superior cerebellar arteries, the same structures were involved as in the previous two cases. They differed from the first two cases in that there was less extensive implication of the cerebellar hemispheres and more extensive involvement of the white matter of the cerebellum and the inner cerebellar nuclei (figs. 5 and 6). This may be accounted for by the fact that the deep branches instead of the superficial branches of the superior cerebellar arteries were involved. Of interest are the selective lesion of the brachium conjunctivum in the region of the fourth ventricle in case 5 (fig. 6) and the fact that the medial lemniscus at this level was not involved.

In cases 6 and 7 there was incomplete obstruction of the branch of the superior cerebellar artery which supplies mainly the brachium conjunctivum. The clinical neurologic picture differed little from that in cases 4 and 5, with the exception that in addition to the "cerebellar signs" and sensory disturbances there was implication of the nuclei of the sixth and seventh nerves. In case 7 the cerebellar signs and sensory disturbances were not recorded, as the patient died twenty hours after the vascular accident. Histopathologically, the structures involved were the anterior medullary velum, brachium conjunctivum, corpus restiforme, medial lemniscus, descending mesencephalic root of the fifth nerve, nucleus of the sixth and genu of the seventh nerve, posterior longitudinal bundle and brachium pontis (fig. 8*B*). The cerebellum, except for a small part of the lobulus simplex, was intact. In case 8 the same structures were involved as in cases 6 and 7, except that the nuclei of

the sixth and seventh nerves were spared (figs. 9*A* and *B*). The signs of involvement of the cerebellum were not elicited and sensory disturbances were not present, as the hemorrhage was terminal. In case 9 only the right dentate branch of the superior cerebellar artery was affected, the process resulting in destruction of the corresponding dentate nucleus. Part of the fibers of the brachium conjunctivum in close proximity to the dentate nucleus were destroyed. There were definite signs of cerebellar involvement. This is the only case in our group in which only the branch supplying the dentate nucleus was involved.

In all these cases the red nucleus and inferior olivary nucleus showed evidences of ascending and descending degeneration. The affected red nucleus was generally paler than normal, and its capsular fibers stained poorly (figs. 3*C* and 7*C*). The involved inferior olivary nucleus was also paler than the corresponding opposite nucleus. At times the latter appeared hypertrophied, and the thalamo-olivary bundle stained poorly (figs. 2*B*, 5*D* and 6*C*).

Sensory Disturbances.—These disturbances usually were of the dissociated or syringomyelic type and consisted of a hemihypalgesia and hypothermesthesia of the face and body. All other forms of sensation were intact. In cases 1, 2, 4 and 6 the aforementioned types of spinothalamic sensory disturbances were present. In case 1 the sensory disturbances were most evident in the lower dermatomes. In case 2 the sensory disturbances were also not complete and consisted of hypalgesia and hypesthesia. In case 3 there were no sensory disturbances, as the spinothalamic pathways are not involved in lesions of the mesial branches of the superior cerebellar artery. The changes in the posterior columns were undoubtedly due to subacute combined degeneration. In case 5 the patient perceived the stimulus as cold when either hot or cold was applied to the body. These types of sensory disturbances belong to the group of so-called dysesthesias or perverted sensations observed in association with spinothalamic lesions. In cases 7 and 8 the sensory examination gave unsatisfactory results as the lesion of the superior cerebellar artery occurred shortly before death. In case 9, in which thrombosis of only the dentate branch was present, the spinothalamic pathway was not involved.

In the cases in which spinothalamic involvement was present (cases 1, 2, 4 and 6) the lateral parts of the medial lemniscus (spinothalamic part) were diseased as a result of thrombosis of the superior cerebellar artery. It is to be emphasized that not all of the medial lemniscus is supplied by this vessel. The greater part of the medial lemniscus, except for the spinothalamic component, is in all probability irrigated by a pontile vessel, a branch of the basilar artery. In case 7 the entire right medial lemniscus was practically destroyed. As the patient was

unconscious to the end, evidence of sensory disturbances could not be elicited. In cases 5 and 8 only the lateral parts of the medial lemniscus were involved. Probably the destruction of the medial lemniscus in case 7 was due to an associated thrombosis of one of the pontile branches of the basilar artery or to an anomaly of the branch of the superior cerebellar artery which supplies the brachium conjunctivum and spinothalamic tract in this part of the pons. Worster-Draught and Allen [14] maintained that the spinothalamic sensory disturbances in these patients are due not to thrombosis of the superior cerebellar artery or its branches but to thrombosis of the small pontile branches of the basilar artery. The observations in a large number of our own cases and those of Critchley and Schuster,[17] as well as the other single reports in the literature, do not warrant such conclusions. In cases with no sensory disturbances of spinothalamic origin or in cases with involvement of all forms of sensation, there is a likelihood of some anomaly of the superior cerebellar artery. Critchley and Schuster [17] suggested that the occasional absence of sensory disturbances in patients with lesions of the spinothalamic component of the medial lemniscus may be the result of bilaterality of innervation.

Other Clinical Neurologic Findings.—In addition to the aforementioned symptoms and signs which are typical of the syndrome under consideration other neurologic findings in our cases merit attention. Diminution or absence of the deep reflexes was observed in cases 2 and 4. In case 4 the lesions in the cerebellum were bilateral, but the deep reflexes were diminished on the left side only. Figures 5*A* and *B* show that the lesion was more extensive on the left side. In the pons the right brachium conjunctivum was completely spared in this case. The deep reflexes were absent in two of Critchley and Schuster's [17] cases and also in Worster-Draught and Allen's [14] case. Van Gehuchten [18] expressed the opinion that the diminution or absence of the reflexes is caused not by the cerebellar disease but by damage to the rubrospinal fibers or to the nucleus ruber. Weakness of the extremities, ascribed by some to cerebellar disease, was observed in cases 2, 5, 6, 7 and 8; the concomitant lesions of the pyramidal pathways in most of these cases and in the cases recorded in the literature are probably the cause of the weakness. Vomiting was noted in cases 1, 2, 5 and 8. Dizziness occurred in cases 2, 3, 6 and 9. Disturbances of speech occurred in cases 1, 3, 4 and 6. Similar disturbances were noticed in all of Critchley and Schuster's cases [17] as well as in the case of Guillain, Bertrand and Péron.[13] Nystagmus was found in cases 1 and 6. In

18. Van Gehuchten, P.: L'abolition des réflexes tendineux dans les tumeurs du IVe ventricule. Contribution à l'étude du méchanisme des réflexes tendineaux, J. de neurol. et de psychiat. **30**:201, 1930.

case 6 there was a lesion of the posterior longitudinal bundle; in case 1 such a lesion could not be demonstrated. It is possible that in case 1 the fibers from the vestibular nucleus, which, according to Winkler,[19] pass by way of the brachium conjunctivum to the red nucleus and down again, may have been involved. This may account for the presence of dizziness and vomiting in some cases, although these manifestations may be an expression of diffuse cerebral arteriosclerosis. We cannot account for the absence of nystagmus in the other cases with a lesion of the brachium conjunctivum. In case 6 there was implication of the nuclei of the sixth and seventh nerves, and in case 7 there was involvement of the nucleus of the sixth and the genu of the seventh nerve. The peripheral facial palsy was slight in both cases. Critchley and Schuster [17] found involvement of the sixth nerve in their case 1 and lesions of the sixth and seventh nerves in their case 4. Whether the lesion of these two nuclei was caused by thrombosis of a branch of the superior cerebellar artery is difficult to say. It is possible that the branch supplying the brachium conjunctivum and medial lemniscus at the level of the pons may be anomalous and also supply the nuclei of the fifth, sixth and seventh nerves. The possibility of implication of the pontile branches of the basilar artery which supply these structures must also be considered. In case 2 there was ptosis with narrowing of the palpebral fissure without other evidence of palsy of the third nerve. This may be accounted for by the lesion of the branch of the left posterior cerebral artery, which may have caused injury to the fibers of the third nerve (fig. 3*A*).

SUMMARY AND CONCLUSIONS

Nine cases of closure or obstruction of the superior cerebellar artery are recorded. Homolateral signs and symptoms due to involvement of the cerebellar lobes or the brachium conjunctivum were present in six cases. Involuntary movements of the nature of tremors were noted in only three cases (cases 4, 6 and 9).

Contralateral sensory disturbances were of the dissociated or syringomyelic type and consisted of hemihypalgesia and hypothermesthesia of the face and body. All other modalities of sensation were intact. In cases 1, 2, 4 and 6 such spinothalamic sensory disturbances were present. In the cases with spinothalamic involvement the lateral parts of the medial lemniscus (spinothalamic component) were diseased as a result of thrombosis of the superior cerebellar artery.

In addition to the aforementioned symptoms and signs, which are typical of the syndrome of the superior cerebellar artery and its branches,

19. Winkler: Manuel de neurologie, Haarlem, de Erven F. Bohn, 1927, vols. 1 and 3.

there were other neurologic findings in our cases, such as diminution to absence of the deep reflexes, weakness of the extremities, vomiting, dizziness and dysarthria.

In some of our cases the signs of cerebellar involvement and sensory disturbances could not be elicited because the patients were in an unconscious state, as a result of closure of the superior cerebellar artery or because these signs were obscured by other cerebral lesions.

Complete obstruction of the superior cerebellar artery (cases 1 and 2) destroys the brachium conjunctivum, the mesencephalic root of the fifth nerve, the spinothalamic component of the medial lemniscus, the lobulus anterior, lobulus simplex, lobulus ansiformis crus 1 and lobulus floccularis and part of the cerebellar nuclei (dentate, emboliform and globose nuclei). The lobulus II vermalis, lobulus IV vermalis and lobulus C_2 vermalis in these cases are spared unless both mesial branches of the superior cerebellar artery are pathologically affected (case 3). In the cases of incomplete closure of the superior cerebellar artery, the extent of destruction of the respective structures depends on the degree of the vascular obstruction.

In two cases (cases 6 and 7) there was involvement of the nuclei of the sixth and seventh nerves, probably due to an anomalous distribution of the superior cerebellar artery.

In case 8 there was occlusion of the branch of the superior cerebellar artery which supplies essentially the brachium conjunctivum and the lateral part of the medial lemniscus.

In only one case (case 9) was there selective involvement of the dentate artery, a branch of the superior cerebellar artery.

DISCUSSION

Dr. Colin K. Russel, Montreal, Canada: Occlusion of the superior cerebellar artery is a striking condition, and it was interesting to have a report on this series of cases by Dr. Davison and his colleagues. Unfortunately, from the point of view of the clinical syndrome of the superior cerebellar artery there was only one case in which the patient was capable as a witness and in whom the lesion was sufficiently well confined to the superior cerebellar artery to make observation of it useful. The other cases were clinically unsuitable: either through the disturbance of consciousness the patients were unsatisfactory as witnesses, or as a result of diffuseness and multiplicity of the lesions the cases were unsatisfactory from the anatomic point of view.

With regard to the usually accepted syndrome—loss of sensiblity to pain, heat and cold on the opposite side and dyssynergia on the homolateral side—I feel that it is scientifically incorrect to describe that loss of sensibility as being of the syringomyelic type. It is true that in syringomyelia the patient loses sensibility to pain, heat and cold, but the lesion is in the anterior commissure of the spinal cord and the areas over which sensibility to pain, heat and cold is lost are dissociated. They are not similar areas of distribution. A lesion of the spino-

thalamic tract in the pons, on the other hand, causes loss of sensibility to pain, heat and cold on the entire side below the lesion. I know that the authors have followed Guillain in the description of loss of sensation in occlusion of the superior cerebellar artery, but nevertheless I think it is to be deprecated.

With regard to involuntary movements, in my experience one does not have involuntary movements with cerebellar lesions; there are rather dyssynergic movements. In at least one of the cases that Dr. Davison described, the substantia nigra was involved pathologically, which I think may have accounted for the involuntary movements.

I was rather interested and surprised to find the lesions of the sixth and seventh nuclei incorporated in this syndrome. I thought that these nuclei were supplied by a vessel lower on the stem than the superior cerebellar artery.

Dr. William G. Spiller, Philadelphia: Mills described the syndrome of a lesion of the superior cerebellar artery in 1908. In his case the onset was sudden, with vertigo, nausea and vomiting. Weakness (presumably hypotonia) and ataxia of the upper and lower limbs were present on the side of the body corresponding to that of the lesion. Tremor was observed in both arms but was more intense on the side of the lesion. On the side opposite that of the lesion there were absolute loss of sensation to pain and temperature up to the median line of half the body and face and also numbness. Sensation to touch and deep sensation was not affected. Deafness was present on the side opposite that of the lesion, but the character of the deafness was not determined. Voluntary control of the face was preserved on the side opposite that of the lesion, but emotional movement (laughing) was lost, while no disturbance of the facial movements was observed on the side of the lesion. Exaggeration of the biceps, triceps, patellar and achilles tendon reflexes was present on both sides. The patient, a man, lived about four years after the onset of these symptoms, which persisted unaltered, as determined by Mills, until about three weeks before the man died. He was probably syphilitic. This was the first description of the syndrome of occlusion of the superior cerebellar artery ever made (1908), and this statement has the support of Schuster.

I made the pathologic study but only a brief report of the essential observations and a photomicrograph were included in a paper on disturbance of sensation, which I published in 1915. The pathologic report was sent to Russel and Critchley and was referred to by them. The observations included: a depression in the upper surface of the left cerebellar hemisphere above the corpus dentatum, measuring 2 cm. anteroposteriorly and 2 mm. in width at its narrowest part and widening at the anterior and posterior ends to 5 mm.; atrophy of the tissue above the corpus dentatum as well as of the corpus dentatum itself; small vessels on the upper and anterior part of the left cerebellar hemisphere; degeneration of the upper half of the brachium conjunctivum, of the left mesencephalic root of the fifth nerve, of the left lateral lemniscus, of the area containing the left spinothalamic tract and of the central tegmental tract; diminution in size of the right nucleus ruber so that it was about one-third smaller than the left nucleus ruber and diminution of its nerve fibers, and lymphocytic infiltration of the piaarachnoid suggesting syphilis. The left medial lemniscus and the posterior longitudinal bundle were not involved.

The case described by Guillain, Bertrand and Péron resembles closely in its symptomatology the case reported by Mills, and in its pathology, the observations which I obtained. So does the case reported by Russel, only in his case have I found mention of impairment of emotional expression with preservation of voluntary movement on the side of the face opposite that of the lesion, as in Mills' case, but the impairment was less intense in Russel's case. This sign may be the result of the diminution of muscular tone.

In the six cases reported by Critchley and Schuster the lesions and symptoms were extensive. In all Schuster's cases the medial lemniscus was degenerated. It appears that an additional artery was involved.

Davison, Goodhart and Savitsky reported an unusual number of cases—nine—in some of which the condition was complicated by other vascular lesions. I have no doubt that in many cases in which both cerebellar and cerebral arteries were involved the importance of involvement of the superior cerebellar artery has been overlooked by other investigators and no attempt has been made to determine the cerebellar artery involved. Davison and his co-workers did not find tremor a frequent sign (it was present in only three of their eight cases), and there appears to be doubt whether tremor can be attributed to involvement of the brachium conjunctivum and corpus dentatum. It is interesting to note that in only one case was the dentate branch of the superior cerebellar artery supplying the corpus dentatum affected alone. Schuster expressed the belief that the branch supplying the area of the brachium conjunctivum of the pontile tegmentum has a special tendency to disease.

In only four of the cases (1, 2, 4 and 6) of Davison, Goodhart and Savitsky was the syringomyelic dissociation of sensation suggestive of involvement of the spinothalamic tract present. All other forms of sensation were spared in these cases. This probably would not have been true in case 7 if the patient had not been unconscious until death, as the medial lemniscus was destroyed.

Dr. Israel Strauss, New York: Which one of the patients came from my service?

Dr. Charles Davison: The first one.

Dr. Israel Strauss: The first patient presented, in whom the condition was definite so far as the pathologic process was concerned, was in my service before being sent to the Montefiore Hospital. At the time he was in my service the clinical picture was definite, and the diagnosis was made on the basis of clinical symptoms. I believe that this patient later while at Montefiore Hospital received a cerebral insult which probably complicated the picture, but at the time the man was first observed the clinical syndrome was so definite that the diagnosis was easily made. The report on that case as observed at that time is now ready for publication, and, thanks to Dr. Davison, the pathologic report which he gave today is available.

Dr. Charles Davison, New York: I have nothing to add except a word about involuntary movements. The involuntary movements noticed in some of our patients consisted of tremor. Other observers (Guillain, Critchley and Schuster, and Worster, Draught and Allen) reported twitching movements. These tremors may be due to lesions of the dentate nucleus, or disease of other pathways or structures may be responsible for the tremor. Two of Critchley and Schuster's patients had involvement of the nuclei of the sixth and seventh nerves. Whether involvement of these nuclei was due to an anomalous distribution of the superior cerebellar artery or to involvement of the pontile branch of the basilar artery is difficult to say.

NATURE OF DELIRIUM AND ALLIED STATES

THE DYSERGASTIC REACTION

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It is the purpose in this presentation to consider the nature of delirium as it is revealed through analysis of the form and content of the psychobiologic dysfunction. The form of delirium has been described by others.[1] In this article the content will be the primary issue, and the form will receive only preliminary consideration. The study has been made to determine to what degree content may be correlated with (1) the specific type of noxious agent and (2) the individual equipment and experience of the subject.

Disorders of mental function due to a change in the brain tissue may prove permanent or may be transient with presumable restitution of the cerebrum. Disorders of the latter variety are the topic of this study. Unfortunately no single or satisfactorily inclusive term to designate this class is in general use. Adolf Meyer[2] proposed the term "dysergastic reaction"[3] for the disturbances "due to disorders of the nutrition and circulatory support of the brain (the effects of poison or abnormal nutrition, anemia, hyperemia and oedema)." It embraces

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1. (*a*) Bonhoeffer, K.: Die symptomatischen Psychosen im Gefolge von akuten Infectionen und inneren Erkrankungen, Leipzig, Franz Deuticke, 1910, p. 94. (*b*) Krisch, Hans: Die symptomatischen Psychosen und ihre Differentialdiagnose, Abhandlungen aus der Neurologie, Psychiatrie, Psychologie und ihren Grenzgebieten, Berlin, S. Karger, 1920, p. 9. (*c*) Die organischen einschliesslich der exogenen Reaktionstypen ibid., p. 60. (*d*) Dannemann, A. C.: Nervous and Mental Reactions to Veronal with Report of a Case of Chronic Veronal Poisoning, J. Nerv. & Ment. Dis. **69**:33 (Jan.) 1929. (*e*) Diethelm, O.: On Bromide Intoxication, J. Nerv. & Ment. Dis. **71**:151 (Feb.) 1930.

2. Meyer, Adolf: Notes on the Dysergastic Reaction, unpublished material.

3. δυσ conveys a notion of hard, bad, ill, poor or working badly under difficulties. εργασια implies work, toil or activity. It is used by Meyer to indicate mentally integrated functioning.

"exogenic psychoses,"[1c] "symptomatic psychoses,"[4] acute delirious mania,[5] "toxic-infectious psychoses,"[6] "infective-exhaustive psychoses,"[7] "deliria of fever"[1a] and "drug delirium."[8] Such an inclusive term has advantages, and in this discussion the terms delirium (in its broadest sense) and dysergastic reaction will be used interchangeably.

METHOD AND PLACE OF STUDY

The patients were studied at the Henry Phipps Psychiatric Clinic, the Johns Hopkins Hospital, the Maudsley Hospital and the New York Hospital. Some selection was imposed by the very fact of admission, since patients had to be sufficiently ill to warrant hospitalization. Moreover, of the patients admitted only those were chosen whose cases were of a type that would afford an opportunity for careful study. A variety of precipitating agents or factors were represented. It was considered of definite advantage that the protocols of many of the cases were made by others than ourselves.

The problem was approached as follows: 1. The behavior of a group of 106 patients with dysergastic reactions was observed, and the factors which exerted an influence on the course of the reaction were recorded. 2. By selection of certain common behavior disturbances of the dysergastic state, the extent to which the same type of disturbance may be precipitated by specific noxious agents was studied. 3. A series of patients each of whom had suffered repeated dysergastic reactions induced by different agents was selected for investigation. Any constancy of behavior observed in the same subject during each of several attacks of illness was attributed to personal equipment and experience. 4. The extent to which personal traits shaped the form and content of the dysergastic reaction was established by selecting a series of patients in whom distinctive individual features could be investigated.

The precipitating noxious agents in the cases were:

Agent	No. of Cases
Alcohol	23
Alcohol complicated by some other factor (such as heart failure)	7
Bromide	9
Lead	2
Copper	1
Barbital sodium	1
Barbital	3
Heart disease with circulatory failure	9

4. Bonhoeffer,[1a] Krisch.[1b]

5. Hanes, Edward L.: Acute Delirium in Psychiatric Practice with Special Reference to So-Called Acute Delirious Mania (Collapse Delirium), J. Nerv. & Ment. Dis. **39**:236 (April); 311 (May) 1912.

6. Hoch, August: The Problem of Toxic-Infectious Psychoses, New York State Hosp. Bull. **5**:384 (Nov.) 1912.

7. Haviland, C. Floyd: The Relation of Manic-Depressive Insanity to Infective-Exhaustive Psychoses, New York State Hosp. Bull. **5**:260 (Aug.) 1912. Brown, Sanger, 2d: On the Interpretation of Symptoms in the Infective-Exhaustive Psychoses, J. Nerv. & Ment. Dis. **43**:518 (June) 1916.

8. Hoch, August: A Study of Some Cases of Delirium Produced by Drugs, Rev. Neurol. & Psychiat. **4**:83 (Feb.) 1906.

Agent	No. of Cases
Exophthalmic goiter	4
Uremia	2
Diabetes	1
Eclampsia and toxemia of pregnancy	4
Head trauma	4
Cerebral syphilis (meningovascular)	2
Encephalitis lethargica (nonepidemic)	1
Convulsions of undetermined origin	2
Rabies	1
Sydenham's chorea	4
Postoperative state	9
Pyrexia of undetermined origin	4
Infectious arthritis	1
Bacteremia caused by Streptococcus viridans	1
Malaria	1
Typhoid fever	1
Infective exhaustive states (postpuerperal)	2
Carbuncle	1
Primary anemia (Addison's)	2
Mixed syndrome of nutritional deficiency (pellagra-like)	4

One hundred and six cases and twenty-seven different etiologic agents were reviewed. The largest groups of dysfunction were those precipitated by alcohol (30 cases), circulatory failure from myocardiac disease (9 cases), postoperative state (9 cases) and bromide (9 cases).

In no instance do the effects of drugs considered in this study refer to the "acute" or short-lived reaction to a moderate amount. Here are included only the effects of prolonged or excessive use, resulting in more or less fully developed delirium.

In about three fourths of the total number of cases the duration of maximal disturbance was approximately three weeks. In the remaining one fourth some patients were ill for over a month and the remainder for many months. With the exception of those in whom the dysergastic reaction was an incident in the course of a more ominous disintegration of personality, all were well within a year.

Certain difficulties inherent in the nature of delirium were encountered in recording observations. Variability was the most constant feature of the reaction. There was a strikingly wide range of functional disturbance in short periods of time. Some of these disturbances disappeared while an attempt was made to study them, whereas the occurrence of others may have been provoked by leading questions of the investigator. The persistent search for a functional defect might therefore have been frequently rewarded by its production. Consequently a detailed statistical analysis was considered to be fruitless if not actually misleading.

In the first section of the paper the main purpose is to demonstrate whether or not there is a specific relationship between the noxious agent and the nature of the reaction. For this reason certain simple non-individualized experiences are discussed, detached from the settings in which they occurred. They were found frequently and apparently arose from backgrounds common in human experience. No serious distortion or confusion results from considering them in this detached

way, even though in doing so some of the significance of disturbance of motility and hallucinatory content has been lost. Moreover, such an arrangement is justifiable for purposes of general orientation.

In the second section the content of the dysergastic state dependent on more individualized experiences is presented. Here a conception of the setting is essential, and detachment from the context would necessarily render the dysfunction meaningless for the purposes of this study.

RELATION OF NOXIOUS AGENTS TO THE REACTION

PHYSIOLOGIC FUNCTIONS

More or less general dysfunction manifest on the biologic level of integration was invariable. Manifestations which were almost always present were: some degree of restlessness; tremor of the hands, feet, face, tongue, eyelids and head; defective sphincter control, especially of the bladder; sleeplessness or poor sleep, and a temperature of approximately 100 F. or more, even in those without demonstrable infection. As a result of restlessness and friction against the sheets the bony prominences of the extremities were reddened, chafed or even more seriously involved. Prostration occurred in the extremely restless patients.

In addition to the dysfunction of the smooth muscles and glands that accompanied infection and intoxication, the somatic accompaniments of fear, rage and horror, such as profuse sweating, pallor, flushing, tachycardia, pilomotor responses, nausea, constipation and diarrhea, were commonly in evidence. Most patients had a poor appetite and, unless carefully nursed, a soiled, dirty tongue and foul breath.

Paraphasia was less common, though slurring speech was frequently noted. Defects in accuracy in stopping and starting, with failure in rapid movements, were seen in unsuccessful attempts to accomplish skilled acts with the hands and in the staggering gait. Several patients had difficulty in swallowing. The tendon reflexes were inconstantly altered and the superficial abdominal reflexes were frequently diminished or even absent. Among less frequent accompaniments were pupillary changes, such as sluggishness of response to light, poorly sustained lateral deviation of the eyeball (nystagmus) and slight congestion and edema of the optic nerve. Four patients complained of diplopia (bromide, 2; alcohol, 1; postoperative state, 1). The occurrence of these somatic changes bore a close relation to the degree of general disturbance and no specific relation to the etiologic agent.

However, in patients with certain pathologic syndromes such as typhoid fever, exophthalmic goiter and injury to the head, the usual local and general derangements accompanying such states were superimposed on the aforementioned manifestations.

PSYCHOBIOLOGIC FUNCTIONS

Nature and Extent of Clouding.—There were in every case some difficulty of grasp and clouding of consciousness. The degree of these defects differed greatly from patient to patient and often from one minute to the next in the same person. Though grasp was sometimes so adequate as to allow complete mentation for shorter periods of time, sustained effort inevitably brought defects to light. In four fifths of the patients it was sufficiently impaired to lead to gross disorientation at some time. Though constantly changing in degree, at periods during the illness attention was poorly sustained, concentration was difficult or impossible and thought was painful, labored and often disconnected. Questions were grasped with difficulty and answers were diffuse, rambling and often beside the point. The memory of recent events was poor and that of remote events was fairly intact, although often vague. Retention was poor, and calculation was usually bad. The 100 minus 7 test was performed slowly, with dwindling and perseveration, when attention could be sustained long enough to attempt such an operation. The ability to recount an episode was poor, the point being missed and the content muddled. Fatigability was excessive. Patients who ordinarily had the ability to perform unfamiliar or relatively complicated tests now failed in all except those that were simple or familiar. Some patients were easily induced to read from a blank sheet of paper or to see fairly elaborate pictures in blurred ink spots. In fact, increased suggestibility was commonly encountered and was evident through the whole range of functional defects. Disturbance in all the aspects of form and content of the dysergastic state was usually more marked in the latter part of the day, during the night and for a short time immediately after awakening in the early morning. In the middle of the day the patients were commonly best integrated. Moreover, patients in the stage of convalescence often continued to be disturbed at night for some time after their state appeared to be normal during the day.

Restlessness.—As already mentioned, restlessness was invariably present and ranged in degree of complexity from highly coordinated and apparently purposive acts down to the most simple movements (tremor and subsultus tendinum), in the production of which psychobiologic components played a subordinate or minimal rôle. As might be expected, with increased confusion the number of more coordinated, apparently purposive movements diminished. It was possible to group movements according to the degree to which they were adapted to some more or less intelligible end. The ability to perform complicated movements corresponded closely with the capacity for sustained attention.

Low in the scale came tossing and turning, arrhythmic squirming, kicking and rubbing of the nose and other parts. A large number of

patients threw off the bedclothes and seemed intolerant of any covering. Sudden, rapid, jerking, birdlike movements of the limbs, of the trunk and especially of the head were characteristic. Another common type of movement was an aimless flopping, often of large amplitude, which caused the skin of the knees, elbows and ankles to be chafed and inflamed. Such behavior was often associated with an irritable, aggressive mood. Picking and fumbling with the bedclothes and uncertain reaching, groping movements were generally observed in those who were most ill.

Restlessness of a more complex nature, such as activities of investigation, were a noteworthy feature in about one third of the patients, though not specially evident in any particular group. Patients searched under the pillows and sheets, looked under the bed and under the table and came out into the hall and peered around the door. The expression was often absorbed or perplexed and inquiring and sometimes apprehensive and fearful. They were often unable to give an explanation of their actions, or the explanation seemed inadequate, as, "I thought my husband might be under the bed," which was the explanation offered by a patient with circulatory failure from myocardiac disease.

Miming of familiar or occupational activities was well defined in 13 patients, and, in minor forms, was present in many more. The miming was of varying degrees of elaboration, usually consisting of simple and familiar activities of sewing, cutting cloth, nursing a baby, telling a rosary or chewing gum. A greater degree of elaboration was seen in a patient who "drove his car" and in another who decapitated and consumed a boiled egg. The agent in these 12 cases was alcohol in 5 and encephalitis, typhoid fever, postoperative state, bromide, barbital sodium, head trauma, and exophthalmic goiter, in 1 each.[9]

No sharp distinction could be drawn between the preceding reactions and those of the following type: Two patients, in both of whom the illness was precipitated by head trauma, sustained in an automobile accident (1, in addition, was an alcoholic addict) and elaborately relived the scene of the accident, attempting with great exertion to extricate themselves from the imaginary wreckage with every show of vivid fear. Another patient (bromide) had a police record and fancied that he was involved in a bootlegging drama, about to be put "on the spot," and enacted a scene rich in the activities of fear and defense. Another patient (barbital) built a bathing platform and jumped from the top of a table onto the floor, which he believed to be a lake.

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9. The data throughout have been arranged so that the description of a given dysfunction is followed by a list of the different types of cases in which the defect was observed. It is not to be inferred that the defect described was present in these types of cases alone. In fact, through this arrangement the variety of precipitating factors that may give rise to a given dysfunction is illustrated.

Such activities, which may be regarded as akin to familiar or occupational activities, merge into a third common type of motility disturbance, which includes reactions to hallucinatory experiences and delusional ideas. For example, 1 patient desired to go out into the adjoining room because he was sure his relatives were there. In other instances the misinterpretation of another patient's voice as that of a relative or of an enemy caused a dramatic reaction, with the expression of fear, flight or fight. Such actions were often intelligible when viewed in relation to their settings. One patient (barbital) in rushing to his brother's defense dashed himself against a wall and injured his head severely. Another (alcohol), after wandering uneasily over the greater part of England, ultimately fled to France, where accusatory voices uttered threats that he would be hung from an airplane. The most extreme forms of motility disturbance, including frenzy, were those in reaction to fear and hallucination.

Mood.—The most common mood was a dreamy, dazed state which was labile and readily merged or was rapidly transformed into one of irritability, excitability, apprehension and fear. The characteristic states were those of doubt, uncertainty, perplexity, puzzlement, strangeness, isolation, anxiety, mistrust and definite suspicion. These states were reflected in a drifting, vague type of talk, often with moaning, whining, repetitions, expostulations and supplications. In the sicker patients speech was reduced to a barely audible and unintelligible mumble. A few examples of frequently made statements are:

1. Exclamations of fear and supplication. "Oh, Oh!"; "Oh, my God!"; "Oh, God—Oh, my goodness!"; "Oh, my!"

2. Statements indicative of puzzlement and concern: "Where am I?"; "I am all mixed up"; "I must get straightened out"; "My mind is muddled"; "I must go —...

3. Statements indicative of concern over self or relatives: "How is my father (mother)?"; "I feel something dreadful is going to happen"; "I wonder what happened to —"; "I wonder where — is"; "I wonder where my husband is."

4. Definite expressions of fear and calamity: "Is my baby dead?"; "Is my husband (wife) dead?"; "— has been killed"; "When are you going to kill me?"; "My husband (wife) is being killed!"; "I will be killed tonight"; "Oh, save me"; and, on a more protesting note, "I haven't done anybody any wrong."

Great lability of mood with rapid changes was the rule. Though a state of indifference was sometimes encountered the majority of patients were deeply stirred emotionally and were depressed rather than in a happy, jovial mood. Several patients (alcohol) had a devil-may-care attitude alternating with one of fear. It was common to see

a patient euphoric, then suddenly weep bitterly for an apparently trivial reason and then once more, in the course of a few minutes, become euphoric and jovial. This extreme variability makes precise statements as to the frequency of elation or depression impossible, but if one takes the prevailing mood as the criterion a euphoric and often grandiose state was evident in 14 patients (alcohol, 8, and exophthalmic goiter, head trauma, eclampsia, postoperative state, cerebral syphilis and circulatory failure in myocardiac disease, 1 each). Ten patients talked of suicide (postoperative state, 1; circulatory failure from myocardiac disease, 1; alcohol, 2; bromide, 1; 5 of the aforementioned series). One patient (alcohol) who made a suicidal attempt was predominantly euphoric, though impulsive. Suicidal attempts were made by 7 patients (alcohol, 2; circulatory failure from myocardiac disease, 2; lead, 1; eclampsia, 2).

Fear was studied in greater detail. Anxiety, apprehension or frank fear was noted in most cases and was often accompanied by such physiologic manifestations as sweating, pallor, trembling, dilated pupils and tachycardia. In many, fear was the predominant affect throughout. For simplicity of presentation the patients have been divided into three groups: (1) those showing great fear; (2) those showing moderate fear, and (3) those in whom fear apparently was not very great or was definitely absent, but in whom it might have been expected from other circumstances, for example, a man who imagined that there were snakes in his continuous bath.

1. For inclusion in the first group it was considered necessary for the patient to have given indubitable testimony of great fear, such as an obviously terrified appearance, cowering, screaming or some other performance which left no doubt about the mood. Fourteen patients were included (alcohol, 5; arthritis, 1; bromide, 1; circulatory failure in myocardiac disease, 2; postconvulsive state, 1; exophthalmic goiter, 1; eclampsia, 1; barbital, 1; chorea, 1). The personality of 3 of these patients appeared to be in no way unusual, 2 were feebleminded, and the data on 3 were inadequate to justify any conclusions. Six patients had definitely abnormal personalities. These may be described briefly as follows: One patient was "unusually" shy, timid and sensitive and had no friends; he had attempted a hold-up and had a police record of other offenses. One suffered from enuresis and was "always easily upset by noise and excitement." One was "quiet, seclusive and noncommunicative and had no friends." One patient "lacked confidence" and was "boastful" and "very suspicious." One was "seclusive, moody and morose" and one was "pathologically suspicious" and "nervous."

2. The group showing moderate fear was by far the largest and will not be further discussed.

3. There were 12 patients in the group in whom fear was not present to a marked extent or was definitely absent when it might have been

expected. In 5 slight fear was present (alcohol, 3; copper, 1; encephalitis, 1). In 7 fear was absent (alcohol, 5; pellagra, 1; pyrexia of unknown cause, 1). In none of these 12 patients were there personality qualities of the type noted among the 6 who showed great fear. Six patients did not appear to be unusual in any way, but 6 had definite qualities which can be described briefly in the following terms: One patient was "of a very even disposition, a great talker and always ready to help." Another was "happy-go-lucky and cheerful," and another was friendly and sociable, the life of the party and "never afraid of anything or anybody in his life." One patient was "indifferent in face of defeat or danger" and was described by relatives as the type of man who "stands up for himself," "not worrisome" and "even tempered"; another was "aggressive and selfish but very sociable," and another was "jolly and sociable and possessed good self confidence."

The fear states were for the most part comprehensible, given the proper setting. This, however, was not always the case. For example, a man with alcoholism, aged 39, had recurring states of fear lasting for about two minutes, for which he could give no satisfactory explanation. Another man with alcoholism, aged 59, had somewhat similar recurring attacks of fear of equally unexplained origin which were not so rhythmic as those of the former. Both patients were accessible and were able to bear witness.

Misinterpretations and Illusions.—Simple misinterpretations sometimes became the starting point of delusional beliefs or were woven into and helped to confirm those already present. The particular elaboration depended on the individual make-up and the history of each patient. The following statements and descriptions are illustrative of the misinterpretation of somatic sensations: "they are breaking me to pieces" (painful arthritis), "monkey sitting on my feet" (alcoholic neuritis; patient in a wet pack), "feet cut off" (posttyphoid state; painful feet), "frog squeezing my hand" (alcoholic neuritis), "tongue cut off" or "maliciously burned" (sore tongue in postoperative state), limbs painful owing to "dog-bite" or to wearing of "tight shoes" (toxemia of pregnancy), backache due to "snake-bite" (alcohol), "bitten by a fish" (alcohol) and "seated in a burning boat" (carbuncle on the buttock).

In these statements there is evidence of elaboration and fabrication and, in some instances, of a paranoid quality. The last had its origin in the misinterpretation of two forms of sensation, one having to do with equilibration (boat) and the other from the skin of the buttock (burning).

The contributions made by disordered equilibratory function in the derangement of the highest integrative functions were frequent. The statements of patients who described themselves as being in or on some moving object are as follows: in a "moving elevator" (alcohol), "train

or boat" (postoperative state), "auto" (alcohol), "airplane" (postoperative state), "ship" (postoperative state and toxemia of pregnancy), "elevator" (chorea) and "burning boat" (carbuncle on the buttock).

The distinction between a delusional belief and the metaphorical statement "as if" in some cases was hard to draw and would often be a matter of individual interpretation. Such interpretation became more difficult when faced with such a statement as "I am floating in air" (exophthalmic goiter), and there was a complete series from sensations such as "going round in a circle" (arthritis), "the house is going round" (convulsions of undetermined origin) and "I am going round" (infection) to frank statements of bewilderment and puzzlement, such as "I am all mixed up" (chorea).

Disturbance in the function of a receptor organ increased misinterpretation in 4 patients (long-standing unilateral tinnitus, 2; homatropine hydrobromide dropped into the conjunctival sacs, 2). The former asked repeatedly whether some one was knocking at the door or whether the rustling of clothes of some one standing behind the door had been heard. In every instance these sounds were referred to as arising from the side of the affected ear. During lucid intervals and when well the noises in the head were properly evaluated. In an analogous way, 2 patients who from time to time had experienced visual hallucinations but who happened to be free from hallucinations when homatropine hydrobromide was instilled were induced to misinterpret pictures held before them or even to fabricate visions after their ability to accommodate became impaired by the instillation. Such effects are perhaps allied to those observed in some patients with defects in accommodation and to the visual hallucinatory effect induced in other patients by pressure of the thumb on the eyeball.

The readiness with which hallucinations were induced in dysergastic patients when the lights were dimmed or when the patients were exposed to sounds having no easily determined relation to the immediate environment may have a similar basis. It appears that factors making discrimination more difficult increased the incidence of misinterpretations and hallucinations. These included any new, rapidly changing or complex situations. For example, 1 patient became very restless, anxious, apprehensive and muddled when moved from his own room to the roentgen ray room. It required considerable reassurance after he had been returned to his room to allay his fears.

Another patient began to mutter as soon as the lights were put out. A feebleminded patient who had a similar experience interpreted it as being due to a spell cast on her. "Please don't put out the lights" was a frequent request of patients. Several patients had visions only at night which disappeared when the lights were on. Several others became more nearly normal when visited by close relatives and had a relapse

when the relatives left. A presbyopic woman suffering from exophthalmic goiter showed an analogous defect. She stated that she saw large numbers of small animals—notably, diminutive foxes and stoats—on her sheets. These sometimes could be shown to have an illusional basis, for when the sheets were moved beyond the range of her presbyopic defect she saw them no more, and said (correctly) that there were only little spots on the sheet. When asked what she saw under a bed across a darkened ward she misinterpreted the somewhat shiny bedpost as a fish. When an electric torch was flashed on this bedpost she at once (somewhat apologetically) described it for what it was. The content of the hallucinations under such circumstances was pieced together from bits of the experience of the patient and was sometimes given continuity or plot by his fears and hopes.

The ability to appraise spatial proportions properly was disturbed in some. Thus a patient with alcoholism said: "The room gets smaller and smaller all the time; it is at least half smaller than it was a week ago." "Everybody seems high and thin and narrow," said a patient on two admissions because of circulatory failure from myocardiac disease. Another patient with alcoholism said: "I am lying straight up in bed."

Common environmental objects were the usual bases for misinterpretation. Thus, the bedcover was thought to be a coat which the patient attempted to put on; a patient while in a wet pack said he had his hands in his pockets; immersion in the continuous bath was evidence of having been thrown overboard; a fold in the counterpane became a fish; the rubber tubing of a stethoscope was a snake (alcohol); the hand on the clock on the wall was taken by 1 patient to be an arrow of dreadful significance pointing at him (bromide); the window was a door and a paper was a knife (barbital); the shiny leg of the bed was a fish (barbital sodium); the bedcover was a napkin; the room was a prison cell because of the bars (postoperative state); the ambulance was a hearse and the stretcher a coffin (postconvulsive state); the radiator was a radio (following a convulsion in a patient with neurosyphilis); the sheets were referred to as trousers (head trauma); a night-light became a part of a machine for electrocution, and waterpipes were mice (circulatory failure from myocardial disease).

Thirty-two patients misidentified people about them. Usually there was hardly more than a vague statement of recognition, such as "Yes, I have seen you before somewhere;" "She is a lady who was down here for a while;" "When did I see you before?" "I have seen you somewhere before," often spoken in a manner of inquiry which would leave little doubt that some confirmative response was anticipated. Furthermore, when the patient was muddled and disinclined to make an effort, it seemed to be difficult to give a dogmatic denial when confronted by

the examiner's provocative question, "Haven't you seen me somewhere before?" Apart from vague attempts at recognition and interpretation the most common mistake was to "recognize" relatives among members of the hospital staff. Some patients went more afield; for example, an attendant was a detective (circulatory failure from myocardiac disease); an old man was a baby (bromide); a physician was a lawyer; students were insurance agents (alcohol); a physician was a priest (exophthalmic goiter); nurses were "impertinent maids" (exophthalmic goiter) and colonial dames (uremia). Agents in other cases in which misidentification occurred were: encephalitis, 1; alcohol, 4; pellagra, 1; trauma, 2; postoperative state, 2; eclampsia, 1; fit, 1; bromide, 1; convulsions of undetermined origin, 1; puerperal state, 1; circulatory failure from myocardiac disease, 2; malaria, 1; pyrexia, 1, and barbital sodium, 1.

Hallucinations.—Visual hallucinations were most common and were experienced by 72 patients. The figures are only approximate, because many of the experiences classed as hallucinations might as properly be listed under misinterpretation, and no doubt many hallucinations took place which were not recorded. On the other hand, the records of the various hallucinatory experiences are comparable as to the degree of care with which they were noted.

A large proportion of patients said that they had experienced at some time during the illness a type of visual hallucination that seemed to be uttterly devoid of personal implication. For example, a series of detached pictures made up of moving figures passed like a changing pantomime before the bed. One woman's description was of people who "silently come into the room through the open door and pass by before the foot of my bed. They seem to ignore my presence, make no sound and pass on. They don't annoy me in any way." Another woman described her experience as "a series of scenes on a revolving stage whenever I close my eyes." Such experiences were often mildly entertaining and, as mentioned, were sometimes induced by closing the eyes. The fact that hallucinations occurred when the eyes were closed in an attempt to sleep frightened many patients and made relaxation difficult. Children especially were so troubled.

Fifteen patients declared that they saw snakes (alcohol, 9; chorea, 2; postoperative state, 1; bromide, 1; exophthalmic goiter, 1; rabies, 1). Animals other than snakes were described by 26 patients (alcohol, 4; encephalitis, 1; typhoid, 1; convulsions of undetermined origin, 2; pyrexia, 1; postoperative state, 2; bromide, 2; syphilis, 1; barbital sodium, 1; circulatory failure in myocardial disease, 1; exophthalmic goiter, 1).

The animals seen were numerous; rats, pigs, tigers, hippopotamuses, alligators, elephants, birds, peacocks and horses were most common.

They were usually smaller than the natural size. This type of animal hallucination was not limited to persons with alcoholism, although patients with alcoholism often saw in their hallucinations a variety of animals. For example, 1 patient saw chickens, rats and snakes; another mentioned smoke, frogs, bees, snakes and men; another, snakes, mice, lizards, leopards, men and girls; another, devils, horses, pigs, mice and small men, and another, a big fox, cats, dogs, sea-gulls, snakes, eels and crabs (he had been a seafaring man). A patient with encephalitis saw "animals," "crosses" on the street, horses, cows and pigs. Following a convulsion of undetermined cause 1 patient saw smoke, a large dog, hippopotamuses, small peacocks and an alligator; in a previous attack she had seen "many animals." A patient with typhoid saw water rats, a monkey and "many strange animals." The increased suggestibility of a patient in a dysergastic state was a complicating factor, and it may be that the hallucinatory experiences mentioned are in a measure a tribute to the pertinacity of the examiner. Spontaneous expression, however, also occurred, as "Look, there is a cat" (exophthalmic goiter). Another type of evidence was the motor reaction to hallucinatory experiences, such as reaching out or cowering away. Easily interpreted movements of this variety were observed in 11 patients (alcohol, 6; postoperative state, 2; bromide, 1; circulatory failure in myocardiac disease, 1; barbital sodium, 1). Less easily interpreted movements apparently having to do with fight or flight were also present.

Bugs, cockroaches, fleas and lice were mentioned by 13 patients (alcohol, 6; arthritis, 1; bromide, 2; exophthalmic goiter, 1; chorea, 1; trauma, 1; barbital, 1). In addition, 1 patient in a postoperative state pulled "black and white worms" out of his wound, and a patient with circulatory failure from myocardiac disease complained of "specks" before his eyes which, however, were not interpreted as being animals. In 3 patients (head trauma, exophthalmic goiter, alcohol) insects comprised the only hallucinatory experiences concerning animals.

Vividly colored hallucinatory forms were mentioned by 6 patients and included such phenomena as colored balls, globes, lights and rainbows (alcohol, 3; postoperative state, 1; chorea, 1; barbital sodium, 1). Various objects having an ominous significance, such as coffins, knives, apparatus for electrocution, hearses and crosses, were described (encephalitis, 1; alcohol, 3; circulatory failure from myocardial disease, 1; postoperative state, 1; infection, 1; exophthalmic goiter, 1; convulsions of undetermined origin, 1; lead, 1; hydrophobia, 1; pellagra, 1).

Human beings and ghostlike forms figured in hallucinatory experiences. Usually, ghostlike forms were described. Occasionally they appeared to be more substantial, and 1 patient (arthritis) threw a pillow at an imaginary figure. Such visions usually appeared at night and often when the patient was half awake. The visions included

images of (*a*) relatives (alcohol, 2; bromide, 2; chorea, 1; eclampsia, 1; postoperative state, 1; syphilis, 1; circulatory failure in myocardiac disease, 2); (*b*) various vague figures, notably black men and Chinese (alcohol, 7; arthritis, 1; postoperative state, 1; circulatory failure from myocardiac disease, 2; trauma, 3; convulsions of undetermined origin, 1; eclampsia, 1; bromide, 3; infection, 1; barbital, 1; barbital sodium, 1); (*c*) angels, devils, "ghosts," dead relatives, the "Blessed Virgin" and the "figure of death" (lead, 1; typhoid fever, 1; alcohol, 1; pyrexia, 1; chorea, 1; postoperative state, 1).

Distortion in the size of visual hallucinatory images was common. Both enlargement and shrinkage occurred during the same period of illness; one alone was sometimes evident on the first admission and the other on a subsequent admission, and both accompanied a variety of different agents.

A man, aged 32, had a fit following excessive consumption of alcohol. He complained that "real small men, 2 feet long, are making faces at me," and in the same attack said, "I saw big men shaking fists at me."

A woman, aged 22, who had had convulsions of undetermined origin for several years, was studied on several occasions following a fit. On her second admission she said concerning a "vision," "My aunt looked real big; her face looked real large to me." On her third admission she saw a peacock ½ inch (1.2 cm.) high.

A man aged 67, with myocardiac disease and decompensation, saw "an 18 foot Jew."

A man aged 34, with alcoholism, saw "eagles as large as a room, carrying horses."

A woman aged 38, with alcoholism, eight days after an operation saw tigers and wild animals in her room and a man under her bed. She said, "Everything I saw was big."

A middle-aged Negro, suffering from fever of unknown cause, saw "a little man the size of a water-pitcher, carrying pieces of the wall."

A woman aged 21, suffering from chorea, saw a "flock of angels as small as doves."

A man aged 39, with alcoholism, described large hallucinatory objects in the first part of his delirium and small ones in the latter part of the same period of delirium.

An unmarried woman aged 60, with exophthalmic goiter, saw a great number of diminutive animals on her counterpane: peacocks, foxes and stoats. She also saw a large dog in her room.

A man aged 43, with alcoholism, saw "cats 35 feet long," as well as a whole menagerie of animals.

Auditory hallucinations were described by 44 patients. A few instances of different types are as follows: Ten patients declared they

heard a discussion about themselves carried on in the third person. These conversations were usually of a disparaging nature by plotters scheming the patients' destruction or that of their loved ones. In hallucinations of this type the patients were never directly addressed (alcohol, 1; postoperative state, 1; circulatory failure from myocardiac disease, 3; lead, 1; bromide, 2; exophthalmic goiter, 1; barbital sodium, 1). The voices of relatives were heard by 12 patients who stated that they heard some member of the family talking nearby (chorea, 1; pellagra, 1; alcohol, 2; typhoid fever, 1; convulsions of undetermined origin, 1; eclampsia, 1; bromide, 1; infection, 1; postoperative state, 1; trauma, 1; barbital, 1). Eleven patients complained of direct accusations or threats from unknown persons or plotters or from persons other than relatives (alcohol, 5; lead, 1; postoperative state, 3; chorea, 1; postpuerperal state, 1).

"Voices" of a less defined and vague nature were mentioned by 8 patients (alcohol, 2; convulsions of undetermined origin, 1; eclampsia, 2; postoperative state, 2; circulatory failure in myocardiac disease, 1). "Shooting" in the vicinity was complained of by 8 patients (alcohol, 2; circulatory failure from myocardiac disease, 1; postconvulsive state, 1; postoperative state, 1; exophthalmic goiter, 1; barbital sodium, 1; pernicious anemia, 1). Five patients heard bells and music (postoperative state, 1; postconvulsive state, 1; eclampsia, 1; neurosyphilis, 1; circulatory failure from myocardiac disease, 1). One patient with myocardiac disease and decompensation repeatedly complained of hearing shrieking, and a patient with typhoid complained of hearing babies crying.

Tactile hallucinations were frequently described. Besides the many from which were selected the examples of misinterpretations arising from various pains and paresthesias mentioned earlier, 8 patients complained of tactile sensations of an unpleasant character, such as bugs crawling on the skin (alcohol, 3; circulatory failure from myocardiac disease, 1; chorea, 1; trauma, 1; toxemia of pregnancy, 1; infection, 1).

Fire and burning were referred to by 2 patients with typhoid fever, both of whom said that their loved ones were about to be burned (1 included herself in this). A patient with alcoholism said that the bed was on fire, and it will be recalled that a patient with a carbuncle on the buttock said that he was in a burning boat. One epileptic patient said the room was on fire, while patients with pellagra, typhoid fever and chorea and in a postpuerperal state said that the house was on fire. One patient, whose condition was due to bromide, complained that he had been scalded.

Seven patients complained of hallucinations of unpleasant smells, such as of decaying food and feces (bromide, 3; eclampsia, 1; chorea, 1; phenobarbital, 1; infection 1). Hallucinations of pleasant odors were

never mentioned, and questioning revealed no evidence of their having been experienced. Gustatory experiences were difficult to isolate from olfactory hallucinations. For example, 1 patient complained as she pushed a hallucinatory object from her mouth: "Don't put that onion sandwich in my mouth; I don't like onion sandwich." Moreover, proper evaluation of both tests when the mouth was unclean, as is common in dysergastic states, was not easy.

Many patients simultaneously had more than one type of hallucination. Those who had auditory commonly had visual hallucinations at the same time. Hallucinations of smell and taste were frequently associated, as were tactile, visual and equilibratory hallucinations. No one agent seemed especially disposed to cause multiple hallucinations.

Confabulation.—The term confabulation is restricted in usage here to the expression of a tendency to elaborate, more or less circumstantially, on imaginary happenings and particularly about every-day events. So far as the emphasis is laid on the aspect of embroidery and amplification, "confabulation" ran through a large proportion of the symptoms of the dysergastic states.

This was specially noted in 16 patients, in many of whom confabulation was frequently present both as a "spontaneous" reaction to various happenings in the environment and as a response to questions especially directed to its discovery. Most of the confabulations were relatively simple and often pointless. There were apparently numerous factors which played a part in the disorder, though impaired memory and deficient grasp were common to all patients having this defect. Such universal human motivation as the wish to have a good opinion of oneself and the wish that others should share this high regard was in evidence in the various excuse confabulations. Thus, 1 patient explained away urinary incontinence by the statement that it had been raining and another by declaring that her "water had broken" and that she was to have a baby.

The most frequent confabulations were in connection with familiar activities, such as visits from, and discussions with, friends and relatives (alcohol, 7; alcohol with head trauma, 2; trauma, 2; carbuncle, 1; postoperative state, 1; toxemia of pregnancy, 1; circulatory failure from myocardiac disease, 2).

Many patients insisted that they had to keep important appointments. This may, for convenience, be looked on as a special instance of confabulation. Patients gave it as a reason why they should leave the hospital and seemed to be convinced that this was the reason for their desire to leave (alcohol, 4; trauma, 1; typhoid fever, 1; carbuncle, 1; bromide, 1; toxemia of pregnancy, 1; and circulatory failure from myocardiac disease, 1).

Delusional Ideas and Paranoid Misinterpretations.—The discussion of these manifestations is rendered particularly difficult owing to what is perhaps the most striking of their characteristics. With few exceptions the delusional ideas were transient and ill systematized; unpleasant possibilities merged into definite beliefs and were put forward to be retracted in the same breath and subsequently forgotten and denied. Patients were readily convinced or persuaded that their delusions were ungrounded. However, every patient at some time and to some extent felt himself the subject of persecution or annoyance.

The delusional belief that the subject was about to be killed was formulated by 18 patients. In this group are included only patients who made a definite statement to this effect. The fear of such a catastrophy was put forward tentatively by many others as a more remote possibility. The reactions to this belief were variable, ranging from terror in one extreme to an apparently calm statement of fact in the other. Not infrequently indignation was expressed at the inadequate protection afforded; some prayed pitiably for protection, while others discussed their impending end with solemn ponderous dignity, or in the manner of a person who is the bearer of weighty "inside information" which he is willing to discuss only in dark and general terms. Eleven said they were going to be shot (alcohol, 7; postconvulsive state, 1; typhoid fever, 1; arthritis, 1, and bromide, 1), and 7 were less definite in their ideas of how they would be killed (trauma, 3; barbital, 1; lead, 1; puerperal state, 1; circulatory failure in myocardiac disease, 1).

The delusional belief that the subject was being shot at or was about to be poisoned was expressed by 12 patients (postoperative state, 1; puerperal state, 1; uremia, 1; chorea, 1; circulatory failure in myocardiac disease, 2; syphilis, 1; alcohol, 2; exophthalmic goiter, 1; bromide, 1; pernicious anemia, 1).

The delusional belief that the patient was to undergo some form of physical torture or had undergone such torture (as in the examples of misinterpretation of unpleasant somatic experiences already given) was expressed by 19 patients (arthritis, 1—"broken to pieces"; typhoid fever 1—"feet cut off for a sacrifice"; carbuncle, 1—"hit by a man"; postoperative state, 1—"tongue cut to pieces"; trauma, 1—"bones broken"; exophthalmic goiter, 1—"burned"; circulatory failure in myocardiac disease, 4 and toxemia of pregnancy, 1—"cut up and operated on"; chorea, 1—"hair cut off maliciously"; bromide, 1—"throat cut"; bromide, 1—"scalded," then "throat cut"; alcohol, 5—"electrocuted," "cut up," "operated on," "beaten to death" and "castrated").

The delusional belief that loved ones or relatives were dead or in danger was formulated in 14 cases (barbital, 1; postoperative state, 2;

rabies, 1; eclampsia, 1; postpuerperal state, 1; chorea, 1; encephalitis, 1; exophthalmic goiter, 3; trauma, 1; alcohol, 2).

The delusioned belief that the subject was about to be kidnapped or abducted was expressed by 6 patients (infection, 1; postoperative state, 1; chorea, 1; exophthalmic goiter, 1; barbital sodium, 1; bromide, 1).

The delusional belief that the subject had been robbed was recorded in 9 cases (eclampsia, 1; postoperative state, 1; circulatory failure in myocardiac disease, 1; exophthalmic goiter, 2; alcohol, 4).

The delusional belief that there were plots and plottings, gangs in the vicinity, wars and revolutions was revealed by 45 patients (arthritis, 1; sepsis, 1; infection, 1; carbuncle, 1; eclampsia, 2; postoperative state, 4; chorea, 1; circulatory failure from myocardiac disease, 8; postconvulsive state, 1; trauma, 2; bromide, 6; exophthalmic goiter, 4; alcohol, 10; barbital sodium, 1; pernicious anemia, 1; pyrexia of unknown origin, 1). Since practically every patient expressed some belief in schemes to annoy or persecute him, the group with this type of delusions was limited to patients whose beliefs reached a considerable degree of definition and who talked about these phenomena not as possibilities or fears but as definite happenings in which they (or more rarely their loved ones) were involved. Coupled with talks of plots and nefarious organizations there was often mention of killing of others. However, the majority of patients who believed or feared that relatives were dead did not commonly connect these deaths with such organizations. The efforts of the imagined bodies were directed against the patients themselves. In addition, same patients talked of vague impending or recent calamities; they asked whether there had been an accident or whether persons had not been drowned or stated that the ceiling was about to cave in or that some terrible catastrophe was about to supervene.

Mystic experiences and feelings of passivity were not commonly encountered. An arthritic patient complained that his actions were influenced in a vague indefinable way, and a patient with bromide intoxication said that he felt there was a machine to register his thoughts. A high grade moron in a posttraumatic state complained that his words were recorded on a dictaphone. Since most of the patients who had mystic experiences were young, lacking in experience or feebleminded, further details of the reaction will be considered later.

The sex functions were inconstantly disturbed. Masturbation was observed in patients during dysergastic states accompanying arthritis, lead and bromide intoxication, toxemia of pregnancy and head trauma. One patient with alcoholism showed a marked erotic interest in the nurses and another with alcoholism experienced nocturnal emissions. The more individual aspects dependent on sex will be considered in the following section.

INDIVIDUAL EQUIPMENT AND EXPERIENCE

In the foregoing section disorders of the highest integrative functions have been, with minor exceptions, categorically considered, waiving the underlying individual substratum. In this section reactions will be presented in more individualized terms; e. g., consideration will be centered about the factors of human variation and personal integration.

In the report of cases presented to demonstrate certain features, only the briefest relevant data for which the case was selected and just enough other data to indicate the principal components of the dysergastic state of the patient are included. In no instance, however, are the omissions of such a nature as to distort the selected facts.

Seven patients experienced more than one dysergastic reaction. Whether the etiologic agent was the same or different on successive occasions, the content and form were similar. In the first 3 cases the precipitating agent was the same or similar during different dysergastic periods. The content in each instance was similar.

REPORT OF CASES

CASE 1.—*Hallucinatory experience centered about patient's relation with his mother.*

A male hospital attendant aged 28 was observed during two separate periods of delirium following alcoholic excesses. When well he was timid, sentimental, sociable and submissive. Periodically he drank with companions, and sometimes he afterward continued to drink alone for several days. He had a fully compensated valvular cardiac lesion, though he had been told or had otherwise gained the impression that he might die of a "heart attack" if he were not temperate. During both periods of illness he was uneasy, fearful and depressed. He complained of palpitation and the fear of death and repeatedly sought reassurance. He was filled with remorse for his conduct and the great distress he had caused his mother through alcoholism. During both illnesses the hallucinatory content was about the same. He described the figure of his mother, whom he saw standing at the foot of his bed enveloped in a grayish-white cloak. She was silent and moved but slightly, but from her troubled expression he concluded that his conduct caused her great anguish. The figure appeared only at night or in the early morning. After a week these experiences ceased, and in three weeks the patient resumed work.

CASE 2.—*Two prolonged cardiac dysergastic reactions with special preoccupations about the paraphernalia of hospitals, medical care and death.*

A tailor aged 59 was observed during two separate dysergastic periods precipitated by failing circulation due to long-standing myocardiac disease. The patient was a quiet, timid, somewhat suspicious man who had few interests outside his work, which had occupied him until the onset of restlessness shortly before admission. During the first illness he complained that the doctors were trying to "make him crazy" by giving him medicine. He talked much of murder, stating that his relatives were going to be killed and, on another occasion, were about to kill him. He was suspicious and showed great fear and marked confabulation. He was restless and occupied much of the time with the measuring, cutting and

sewing movements of his trade. Within a month his circulation had improved and his fears and preoccupations disappeared. Three months later, during an acute exacerbation of the circulatory defects, he was readmitted to the hospital. Again he expressed fear of doctors, nurses, operations and medicines. He complained that his family was trying to exterminate him. He shouted "murder" and "police" and between periods of great fear showed again the occupational movement patterns of his daily work.

The repetition of the same experience in the dysergastic state occurred in certain persons following convulsions.

CASE 3.—*Convulsions followed on three occasions by reactions centered about equilibratory disturbances with an admixture of other hallucinatory experiences.*

A married woman aged 21 had fits after the birth of her first child. She continued to have generalized convulsions at approximately monthly intervals. During her first residence at the hospital she was bewildered, stating that she was in an airplane and that "it feels like the ceiling is on the floor." The room seemed to revolve. She also complained of sensations "like electric shocks going through the bed." Some milk spilled on the floor she interpreted as a dog, and she saw two small dolls dancing on the mantelpiece. She also said the room was on fire. During her second admission, a few months later, she saw "things going 'round" and "the ceiling light traveling down to the floor." She felt as though there was a cloud of smoke between her and her surroundings. During the third admission, some two years later, she again described objects in the room as going around and the room as revolving and complained of feeling electricity going through her bed. This time she described a richer variety of animals and mentioned seeing "hippos" and a lion in the ventilator, several rats, a peacock one-fourth inch high, a bird on the wall, a tiger under the chair and an alligator above her. She repeatedly reached out toward these images and would at times discuss them dispassionately, though on other occasions she exhibited fear.

The next 3 cases are examples of similar dysergastic experiences occurring during different dysergastic reactions and precipitated by distinctly different incidents. Case 4 illustrates the occurrence of the same simple hallucinatory experience during four illnesses which took place over a period of thirty years. As in case 5, the content of the hallucinatory disturbance was so simple as to predicate no special experience which even a child might not have had, yet it reoccurred during the illness of the adult period. It is to be noted that in case 4 there were four separate etiologic agents.

CASE 4.—*Similar content in delirium occurring during four illnesses precipitated by four separate agents.*

A trained observer and physician had illnesses with fever at the ages of 8 (measles), 12 (malaria), 30 (tonsillitis) and 41 ("influenza"). He described an experience common to all the illnesses as follows: "I seemed to be unconscious of my body, feeling as though I were suspended in space. I experienced a distressing sense of insecurity. A cloud would come up before me and with a spiral motion shape itself into a brilliant whorl. These whorls made up of golden brown particles sparkled and glistened like snow being blown in a whirlwind. The whorls were revolving in the same and different directions, though any one con-

tinued to revolve in the same direction until it was dissipated." On two occasions, in different illnesses, "brilliantly illuminated green, yellow and red angular crystalline masses shaped themselves into ever-changing patterns like those formed by bits of glass in a revolving kaleidoscope."

The next case exemplifies the incidence of identical sensory experiences induced by different agents.

CASE 5.—*Similar content of delirium precipitated by various agents.*

A laborer aged 32 was in a dysergastic state precipitated by fever of uncertain origin, probably an accompaniment of an infection of the respiratory tract. He was known to drink alcohol periodically and to excess, and he had had long-standing polyarthritis. Sometimes after a severe debauch he had one or a series of generalized convulsions. Neither alcohol nor fits played a rôle in the production of the dysergastic reaction. He was disoriented, muddled and overactive and complained of seeing many animals and devils. He said "everything was upside down and sideways." Two years later he was admitted to the hospital during a series of generalized convulsions which came on after a severe alcoholic debauch. After the fits had stopped he was restless and confused, misidentifying people about him and describing animals and devils talking to each other and laughing at him. He said, "Instead of lying down, I was lying straight up . . . instead of walking straight up I was walking sideways." Within one week he had fully recovered.

In the following case the patient, like the patients in cases 4 and 5, had identical experiences in delirium after an interval of thirty years. Though the dramatis personae and the eliciting agent had changed, the patient's reaction was similar.

CASE 6.—*Identical experiences in delirium after an interval of thirty years.*

A man aged 37 experienced delirium after excessive drinking of alcoholic beverages. In health he was shy, sensitive, lacking in self-confidence and mistrustful. During the illness he stated repeatedly that his wife was trying to poison him with medicine. He recovered after a month and on no subsequent occasion gave vent to any suspicions about his wife's murderous intent. She died some time later. He married again. At the age of 56 he gave up drinking alcohol in any form. At the age of 67, thirty years after the previously described illness, he became ill because of myocardiac decompensation. As an accompaniment of the circulatory failure he became disoriented, apprehensive and restless. During this second attack of delirium, in which alcohol was known to play no part, he was admitted to the hospital. During his stay he again and repeatedly complained that his wife (the second wife) was trying to poison him with medicine.

Two patients had suffered from a mental illness that was not dysergastic several years prior to admission to the hospital. Their reactions during the observed dysergastic state were colored by a mood reaction akin to that which they had exhibited in the previously experienced psychosis. The following history is illustrative.

CASE 7.—*Delirium in a patient with a history of recurrent depression.*

A married woman aged 46 consulted a physician because of ready fatigability and breathlessness. She was advised to have a nodular goiter removed. Following this (to her) alarming advice she became excited, anxious and fearful and was

admitted to the psychiatric clinic because of excessive restlessness and elation. Before the onset of the illness she had been an energetic, active, sanguine person who had always enjoyed good health with the exception of minor illnesses and two periods of excitement requiring hospitalization. The first of the latter occurred when she was 17 and lasted ten days; the second occurred when she was 26 and lasted fourteen days. Both attacks were described as episodes of elation and overactivity, with push of speech and flight of ideas and of sufficient severity to make management of the patient at home impracticable. She had always wanted children but had not had any. Several years later it was observed that the thyroid gland was increasing in size, and subsequently a diagnosis of nodular goiter was made. When told that an operation was essential, there developed a great fear, and soon she passed into a bewildered excited condition. She moved about excessively, was elated and grandiose in talk, said she was like Greta Garbo and had won a prize for beauty and believed that she was in a maternity ward and that she had so many babies there were not enough chairs for all of them to sleep on. She said she was about to marry Professor Einstein and knew "every wise word in every language." She was distractible, talked and laughed excessively and was very active. Moreover, she complained of seeing bugs and maggots, scolded the nurses for their indifference about such breaches of domestic cleanliness and warned them that they would lose their posts were her complaints made known to the authorities. She subsequently had auricular fibrillation, became less active and elated, and died shortly afterward.

The following report illustrates the opposite type of reaction in a patient who was known to have had a severe attack of depression many years before. As in other instances of this type the mood disturbance outlasted the period of disorientation and hallucination.

CASE 8.—*Postoperative delirium in a patient with previous depression.*

A furniture dealer aged 59 became disoriented and bewildered after suprapubic cystotomy performed for the relief of an obstruction due to carcinoma of the prostate. When well he was active, energetic and ambitious, but he worried readily and had had a severe depression of uncertain duration fifteen years before. Shortly after the operation he became restless and suspicious and complained that people were plotting against him and were probably trying to poison him. He complained of being depressed, looked dejected and threatened to commit suicide on several occasions. He was given to much anxious pondering over his affairs, and his speech was replete with self-accusatory and deprecatory utterances. About a week later, with improvement of his general condition, though still dejected he became quieter and talked less about his affairs. However, when last observed, about a month after the onset of the illness, he was still mildly depressed.

Dysergastic states as complications of other psychopathologic states were observed in 4 patients. The following reports are illustrative:

CASE 9.—*Bromide delirium in a woman with paranoid development.*

An unmarried, oversensitive woman aged 35 had been growing progressively more suspicious of fellow workers for two years. She misconstrued their acts as attempts to throw her in an unfavorable light with her employer. She formulated the belief that there was a plot on their part prompted by envy of her position as secretary to the manager. She stated that there were attempts to annoy, slander and irritate her and thus force her to resign from her post. She visited a physician, who, finding her in a tense and anxious state with much pre-

occupation with her problems, gave her bromides. She took the medication regularly and perhaps in large amounts. Some weeks later she became disoriented, was "muddled," found it difficult if not impossible to do her work, was fearful and became resentful of any act done to help her. Moreover, she had visual hallucinations and elaborated delusions of persecution by her fellow workers. After about three weeks this exaggerated state of mistrust and fear subsided, though she continued to misinterpret her surroundings. Six weeks after the onset of clouding of consciousness she could concentrate easily and was clearly oriented but still had a bromide acneform rash. She had no insight into the recent more gross paranoid misinterpretations, and she did not concern herself greatly about her delusions. She viewed her recent experiences in the same way as she viewed the alleged happenings at the office. Several months later she still lacked objective retrospective insight on the topic of her experience in the hospital.

CASE 10.—*Bromide delirium in a man with depression.*

A worrisome clerk aged 49 had suffered from unusually disturbing feelings of anxiety and tension since a minor accident which had befallen him a year previously. Depression became a more dominant feature during the last three months. He was given bromides to relieve restlessness and poor sleep. After several weeks of bromide medication, speech became slurred. Restlessness increased, and he had difficulty in thinking and became muddled readily. He thought persons about him were unduly interested in his affairs. His utterances were those of self-reproach, accusation and depression. After an attempt to commit suicide he was admitted to the hospital. He looked dejected and at times fearful. During the first few days of his stay in the hospital he saw visions of his wife in the garden and confided in his physician the conviction that a large and powerful organization was setting plans to kidnap him. Within a month of cessation of the bromide medication he articulated clearly and no longer saw visions. His fears were less marked and he mentioned no more "plots." However, a mild depression persisted for several months and then gradually disappeared.

Two patients experienced typical dysergastic states as a complication of depression, because of the refusal to eat. The resultant pellagra-like syndromes were characterized by sore mouth, sore tongue, diarrhea, pigmentation and hyperesthesia of the extremities, as well as defects in grasp, hallucinations, fears, suspicions and, presumably because of the underlying affective disturbance, depression which dominated and considerably outlasted the more acute dysergastic phenomena. The following history is illustrative:

CASE 11.—*Delirium as an accompaniment of a deficiency syndrome in a woman with depression.*

A woman aged 46 was admitted to the hospital after four months of depression, loss of appetite, weakness and loss of weight. She came of a family which was comfortably well off and had accustomed herself to beautiful surroundings and expensive habits. She had always been considered "frail," had worried easily and had had occasional attacks of insomnia. She had been mildly depressed during the menopause one year previously. Four months before admission, during the general financial depression, her husband lost his position, and she was for the first time confronted by a series of financial problems. She worried a great deal and was preoccupied by the concerns of making a small amount of money cover expensive habits. She gradually became more depressed at the hazardous

financial state of the family affairs. She thought the situation was hopeless About three months before admission her joints began to swell and a month before there developed nausea and vomiting, speech became slurred and there were sore, red tongue and diarrhea. The depression persisted, and she refused all medical aid.

On admission she was weak and emaciated, with tremor of the eyelids, tongue and extremities. The tongue was inflamed and infected and the hands and feet were slightly pigmented; there were tenderness and stiffening in the joints of the extremities, and numbness and tenderness of the distal portions of the arms and legs. She had peripheral neuritis. She was confused, dejected, fearful and weeping and complained that every one was talking about her. She was restless and completely disoriented and complained that her husband was being accused of wrong-doing. She often announced that "He could not do it . . . he is the son of a Unitarian minister." She was afraid to go to sleep and pointed to "the handwriting on the wall." Visual and auditory hallucinations continued for another two or three weeks. She then became mute for shorter or longer periods. At such times she responded rarely to questions, had a puzzled, fearful facial expression, muttered and stared at the examiner. She resisted movement and was cataleptic. After tube feeding with a diet rich in calories and vitamins, as well as the administration of vitamins intramuscularly, the diarrhea disappeared and she gradually recovered weight and strength and subsequently began to talk and to feed herself. Her spirits improved slowly, and two months after admission, though still dejected, the hallucinations and misinterpretations had entirely disappeared. Five months after admission she had fully regained weight and strength and was in excellent spirits. Some stiffness of the joints of the fingers remained.

Outstanding character qualities, like dominant mood states, lend a highly individual quality to the dysergastic reaction. The utterances noted in the following case are illustrative.

CASE 12.—*Traumatic delirium in a man with outstanding character qualities.*

A successful man aged 65, the director of an educational institution, became unconscious for forty-eight hours following an injury to the head sustained in an automobile accident. For a few days after regaining contact with his environment he appeared dazed, but he had no special complaints. Shortly after that, however, he became suspicious and felt that, although perfectly well, the doctors were detaining him for secret motives.

Before the onset of the illness the patient was an energetic and self-confident man. He was a successful leader and executive, having achieved a position of considerable social and political importance in his community. He was "patriotic," "fearless," "daring in taking risks" and bombastic. An examination of pamphlets written by him revealed an elaborate, rotund style with a generous sprinkling of high-sounding phrases and words. He possessed and cultivated considerable oratorical ability. The conviction that he was being detained became elaborated into one of persecution organized by numerous and always powerful though somewhat varying organizations, the Roman Catholic Church and the governments of India and China being the major interests. Passing cars were driven by agents of his enemies who photographed every movement he made for the benefit of his enemies. At times he was definitely disoriented, and frequently he confabulated. He often boasted of the immense resources at his disposal to cope with his difficult situation; that one sentence of his could seriously affect thousands of business ventures. Men would pay $150 for one hour of his con-

versation. He said: "Must I remain incognito?" (What place is this?) "Would you like me to answer now? This building is a large brick structure purchased by (patient mentions own name) and friends of his and loaned by them to the Johns Hopkins University for temporary and experimental purposes as a hospital." (Spirits?) "All right, how are your spirits?" (How do you feel at present; happy or unhappy?) "I'm being insulted by a shallow-minded and fraudulent pretender to the authorities and privileges of a personal physician; I feel deeply resentful, incurably hostile and uncomfortable." On another occasion he said: (Have you any worries?) "My tremendous business responsibilities and rain of foreign telegrams all day long keep me shut up, keep me always more or less tied, doubtful, laborious and worried, but of all periods of the day, the period when the doctor is in my room is the worst of the twenty-four hours." One night he said: "I must stay awake to protect myself. Your protection is infinitely childish. Look at that open door! This morning my enemies would have killed me but for an accident. As far as your protection is concerned, I am a dead man. Yes, except for my cunning, I am a dead man."

The conditions most suitable for the demonstration of the relation between the personality and the content of the dysergastic reaction were in a patient having a personality with well marked characteristics and a dysergastic disorder of relatively light intensity. The two following cases illustrate how the personality tendencies and the major conflicts mold the content of the dysergastic reaction.

CASE 13.—*Personality tendencies and major conflicts molding the content of barbital delirium.*

A hospital orderly aged 32 was admitted to the hospital because of restlessness, suspicion and terror following the prolonged and excessive use of barbital. In health he was described as being a rigid, high-tempered, sullen man who was suspicious of motives and who had given expression to the theme that "the world was against him." For many years he was known to have washed his hands excessively and to have insisted on unusual cleanliness of eating utensils, commonly polishing his knife and fork on his napkin before eating. He kept his private belongings carefully locked to prevent theft. His intelligence was moderate (a Binet test performed after he had recovered from the delirium gave a mental age of 9½ years). He had taken drugs for "headaches" for an indefinite period and had on occasions become muddled. During such periods he was much on the defensive and had even laid in wait with a revolver for supposed attackers.

The illness for which he was brought to the hospital had lasted only a few days. Throughout this period he was exceedingly aggressive and had impulsively made several suicidal attempts. While rushing to assist his brother who he believed was being murdered he dashed his head against a wall. On another occasion he mistook a towel his brother was about to apply to his head for a knife and expressed the belief that his brother was going to kill him "because he saw I was suffering." He was frequently terrified and had an unreasoning suspicion of almost all events. Among other visual hallucinations he saw two white horses, with a woman on one of them. He complained that there was blood on the sleeve of his bathrobe and spent much time trying to wash this off. Bugs on his towel also afforded him much annoyance. After three weeks he was no longer muddled and became less suspicious. Following discharge he resumed work, but about two years later he committed suicide.

The case just reported also illustrates the sudden impulsive behavior and blind resistance which, as has already been suggested, is sometimes found in defective persons. In a second patient, obsessional activity was demonstrated, and hand-washing became a more prominent feature in the dysergastic condition than it was in normal life.

CASE 14.—*Obsession appearing during a period of delirium.*

A married woman aged 43 had been separated from her husband. After an operation for disease of the gallbladder she became restless and confused. Prior to the operation she was known as a conscientious, perfectionistic type of person, of excessive personal cleanliness and addicted to unessential hand-washing. Soon after marriage her husband had forced her to masturbate him. She reacted to this practice with extreme disgust, and soon afterward a separation occurred. She had subsequently experienced a numb feeling in the right hand. She was very fond of children, but because of her unfortunate marital experience these had been denied her.

During the illness, which lasted about two weeks, she had visual hallucinations, describing "sweet little kewpies" and saying, "I have always wanted a baby. Some people call them unknown babies." Of the nurse in attendance she requested again and again that her right hand be washed. Repeated compliance afforded her little satisfaction.

In addition to outstanding personality qualities, important life problems lend an individual turn to the content of the dysergastic state. The following history illustrates the preoccupation with an important life problem.

CASE 15.—*Cardiorenal disease and delirium with preoccupation about family plottings and marital situation.*

An insurance salesman aged 67 was ill with serious hypertension, arteriosclerosis, myocardiac decompensation and nephritis. A few years before he had married a woman who was considered by his family to be socially inferior. The patient and his family were estranged because of the marriage and his relatives had more than hinted their belief that the wife was "after his money." He had always been a moderately ambitious and punctilious man. Though dapper, he was moody and sometimes depressed. He was more suspicious than the average man in his station in life. During the delirium occasioned by terminal uremia he expressed the conviction that his family were scheming to get his money and to effect a separation between him and his wife. Though unable to formulate his suspicions clearly he said enough and showed by insinuating shakes of the head, half-finished sentences and facial gestures that he was greatly preoccupied by fears for the well-being of his wife and the plottings of his family. As he became sicker the fears were fewer; subsequently he became stuporous and died.

Persons who in health gained much support and comfort from religious formulations and practices commonly gave some religious coloring to the content of their dysergastic experiences. The patient in case 16 is an example.

CASE 16.—*Religious preoccupations coloring the content of delirium of a nurse ill with paratyphoid fever.*

An unmarried nurse aged 42 was ill with paratyphoid fever. When in good health she was deeply religious. She was exceedingly clean about her person and clothes, was perhaps overmodest and overreacted to exposing herself in the presence of others. During the illness she was often much disturbed at night. She said her feet were cut off for a sacrifice (neuritis? thrombosis?). She heard voices calling her "immoral" and thought her family was to be killed and that the house was on fire. She said, "Christ is here. I must kneel at His feet. I saw angels and all kinds of animals looking at me" and, pointing to the wall, said "I can see Jesus on it."

CASE 17.—*Religious trend of delirium in an orthodox woman with exophthalmic goiter.*

A genteel, pious Roman Catholic woman aged 65 had a dysergastic reaction in association with exophthalmic goiter. During the illness she referred to the nurses as "impertinent maids." She mistook the physician for a priest and, according to her statement, believed herself to be in church. She spent much of her time praying and telling an imaginary rosary. Her fingers made the movements necessary to roll the beads as she prayed.

The patient described in case 18 not only had religious preoccupation but wove into the design of her delirium the desire to have a baby or, better, twins. Her fear of convulsions took the form of concern about her husband's well-being.

CASE 18.—*Preoccupation about children and religion in a postconvulsive state.*

A sensitive, timid, excitable, imaginative and religious woman aged 24 was admitted to the hospital in a dysergastic state following eclamptic convulsions. She was described as a person who "had always been afraid of thunder showers." On admission she was excited and disoriented. Later bewilderment was a prominent feature: "When I talk I hear other people talk, I don't know whether the voice is in my own mind or if someone is testing me out." She expressed great fear that her husband was going into convulsions. She described many visions of the Father, Son and Holy Ghost and thought she had given birth to twins. On one occasion she explained the wetness of her bed (incontinence) by saying, "Oh, dear, my water broke."

On recovering, she said: "Everything got twisted up in the delirium and it seemed like I was giving birth to a Christ Child. When I was at school I acted in a Christmas play and that was how the idea must have got in my mind."

In addition to the religious preoccupations, the saying of prayers and the telling of the rosary may perhaps be allied to habitual or occupational movements. The weaving into the content of a dysergastic reaction certain familiar, habitual or occupational, though often highly individual, concerns is illustrated in the utterances of the patient in case 19.

CASE 19.—*Delirium in which recent surgical experiences commingled with the preoccupations of the patient's business.*

A middle-aged, energetic and successful furniture dealer, with "business" as a dominant interest, experienced a dysergastic reaction following an operation for the relief of intestinal obstruction due to a rectal carcinoma. During the illness he said: "And when I sat on the bedpan I could not deliver the furniture. It was all marked and graded; the only thing that was missing was the delivery,

and that caused excruciating pain. They told me they would cut a passage-way for the delivery of that furniture, but the bowels have not worked yet and that is excruciating. . . . Come here, Doctor, I want to tell you how I have suffered in the last two weeks. They told me that if I consented to have a passage cut into the bowel so that the mucus could pass and another to take care of the water, then after a while the normal would return. Now they tell me there is a whole row of telegrams to be answered, and when I sat on the pan to answer the telegrams I wrote out the first few words, but the pain was so intense that I couldn't finish the telegram—and when I looked the telegram wasn't there—not a thing."

In this patient, pain, his recent surgical experiences and the preoccupation of his business were commingled. In several other instances the precipitating circumstances of the illness helped to color the symptomatology. For example, a middle-aged man was having considerable difficulty in paying the instalments on a new house. There was danger of foreclosure and of losing the house and all payments. The man began to drink alcohol for consolation. During the dysergastic state that followed he complained that workmen and foreigners were tearing down his house. Again, two patients with head injury following an automobile accident relived the accidents in fantasy and referred repeatedly to being entangled in the wreckage, asking that it be pushed off.

The factor of sex was significant in shaping the content of the dysergastic reaction. Women, in contrast to men, frequently referred to visual hallucinations of babies and children. They also (especially childless women) described having many children or anticipated their arrival. Actions associated with attending the wants of infants or small children were common.

Eight patients felt themselves to be accused of "immorality." They were women who complained that they were suspected or accused of "loose misdoing" (postoperative state, 4; typhoid fever, 1; bromide, 1; puerperal state, 1; circulatory failure and myocardiac disease, 1).

In contrast to the type of hallucinatory accusations of women, men in no instance in this study complained or referred to accusations of promiscuity, infidelity or extramarital sexual relations. On the other hand, accusations of sexual perversion, notably cunnilingus and various homosexual practices, occurred several times (case 20). Ten patients supposed that their spouses or lovers had been unfaithful to them (alcohol, 3; circulatory failure in myocardiac disease, 2; postoperative state [female], 1; bromide [male], 2; neurosyphilis, 1, and eclampsia, 1). A man with alcoholism supposed that his wife was married to all the nurses; though not complaining of infidelity, a patient with lead poisoning supposed that his wife was against him and wished his death; a man with alcoholism felt that his wife was plotting to murder him; another man with alcoholism, who kept a mistress, thought

that his wife was attempting to murder him, and still another man with alcoholism felt himself to be the object of a homosexual assault by an attendant.

Intellectual development was also a determining factor in the content. In the feebleminded, the young and the uneducated, blind resistance and impulsive reactions to their environment were more common than in those with mature intellect. Similarly, feelings of passivity and mystic experiences were more common in the former than in the latter group; spells were cast, messages radiated from inanimate objects and the content in vividness and cruelty appeared more primitive. Thus a feebleminded patient with alcoholism felt that he had a large amount of electricity in his body and hoped by making passes at the attendant to exert an influence over him. A youthful patient with chorea felt that she was two people and complained of various sensations of bodily distortion. A young woman with repeated convulsions of undetermined origin complained during the dysergastic states following the fits that she had been possessed by a devil and that a curse had been put on her. During these periods she spoke to her dead mother, whom she saw beckoning to her and advising her to come into the other world. A feebleminded patient had a dysergastic reaction after some of her regularly recurring fits. She became disoriented when the light was extinguished in her room and complained that when the lights were put out a spell was being put on her. Another believed herself to be impersonated. A third feebleminded woman, separated from her husband, had a dysergastic reaction after a gynecological operation. She said: "I hear bells ringing. I am a sinner. They are going to cut my tongue out." Later she talked of "burning at the stake." A fourth feebleminded girl, during the dysergastic reaction following a fit, involved herself in anthropomorphism. While she was immersed in the tub the fountain in the garden sent messages to her telling her to beware of certain influences. Being possessed by the devil was a frequent complaint among feebleminded patients with convulsions.

In contrast to these were the sophisticated utterances of a judge who had a dysergastic reaction after an operation. He said: "My poor family! There are always two sides to a thing. It all depends on whether they catch me or not. The Ku Klux Klan will prevent my nurse returning in the morning. I will testify against you all! I have a large family and we will demand an explanation. They can chloroform me or choke me; that will be the only way to keep me quiet."

It was apparent that important urges, strivings, fears, preoccupations and conflicts enacted in the setting of daily life figure in the content of the dysergastic state. As this state has, therefore, some features in common with the dream, a comparison of the relation between the states suggested itself. Further features in common are

the loss of appreciation of time, the richness of visual imagery and the indifference to inconsistencies.

Observations made on patients during the process of awakening bore on this point. Many were more confused, had greater difficulty in thinking and had more slurring of speech on first awakening. A few were subsequently able to recall dreams of situations from which were abstracted the utterances, bits of conversation and action patterns actually noted by the examiner during several minutes after the arousal of the patient. It appeared as though some of the unusual behavior for a period after arousal represented the response to, and was being carried over from, dreams. The difficulties were more marked if the patient had been aroused from sleep by the examiner, though similar defects were noted after spontaneous awakening.

Furthermore, patients commonly employed the words "dreamlike" and "dreamy state" in retrospective accounts of their illness. Such evidence is of doubtful value, since untutored patients describe as dreams widely dissimilar, unusual happenings which are unlike ordinary waking states. However, some patients seemed to be unable to distinguish between dream and waking states. For example, one man expressed his difficulty thus: "Would you wake me up if this is a dream?" Another patient during the lucid interval between periods of confusion and hallucination referred to the delusions of his dysergastic state as incidents that occurred in an unpleasant dream.

The relation of the content in the dysergastic states to that of the dream was further indicated in two instances (alcohol). Both patients had for two or three nights before the onset of frank hallucinations during the day dreamed of the images that subsequently appeared in their hallucinations. In one instance the patient told his wife about these dreams the morning after they occurred. He described vivid troublesome dreams in which animals roamed about. Identical forms subsequently occurred in his waking state as hallucinations. The other patient, a hospital orderly (case 1), complained of disturbing dreams to the physician two days before the actual onset of hallucinations in the waking state. He was a periodic drinker, aged 28, with a fully compensated lesion of the cardiac valves. He dreamed of his absent mother, who appeared at his bedside enveloped in a long robe or sheet. He stated that she looked unhappy because of his excessive drinking. Later the same figure appeared in the hallucinations occurring during the waking state.

When the incidents of a hallucinatory or illusional experience are of trivial significance, the patient soon evaluates his experience. Sometimes a mistaken concept survived throughout an illness but was soon dispelled after recovery.

A teacher, aged 48, during the first three days following an operation for the removal of carcinoma of the breast was given morphine for relief of discomfort. The usual noises of children's play from the street below her window reached the patient's room. During the dream-like state brought on by morphine she visualized these children as cockroaches darting about from place to place, now and then standing on their hindlegs and slapping together their antennae or clawlike anterior extremities. On leaving the hospital two weeks later she encountered the same children at play and was surprised and amused at their actual appearance.

However, the experiences during the dysergastic reaction were in some instances so vivid and their significance to the patient so grave that they remained for long periods in the memory of persons who had otherwise recovered as events which they were convinced either did occur or might have occurred.

CASE 20.—*Long-lasting reaction to an experience of grave significance.*

An artisan aged 44, as a young man was of a frank, open disposition, though shy, sensitive and always lacking in self-confidence. He was fearsome about any new adventure. When he was occasionally depressed he "drank" to cheer himself. He had a sister who had been hospitalized because of an attack of depression. Five years before his admission to the hospital, after a period of prolonged drinking, he had an illness during which he experienced visual and auditory hallucinations. He described how trolley-cars on the street below his window stopped to discharge and take on passengers who projected their heads, looked up at his window and shouted slanderous remarks. Passengers who had alighted, pedestrians and occupants of automobiles and taxicabs stopped, looked up at his window and shouted similar accusations. He left his apartment to seek refuge in a "speak-easy," only to find that the guests made similar though less direct accusations in their conversations with one another. In all instances these slanderous accusations took the form of attacks on his morality, character and integrity, but chief among these were accusations of sexual perversion.

Some days later these alleged actions on the part of the public ceased but the patient moved away from the neighborhood and later from the city. Though there was no repetition of this experience, the patient was haunted by the delusion that he had been exposed publicly.

Five years later, after another prolonged period of drinking, he became delirious and again had delusions that persons about him began to discuss his sexual practices. He attacked one of his acquaintances because of what he believed he had heard him say. During this illness he was persuaded to enter the hospital.

With abstinence his improvement was rapid, and after approximately three weeks he no longer heard people talking about him. It was revealed that the patient six years before, during acute intoxication had engaged in cunnilingus with his wife. He attributed such sexual interest to the influence of the alcohol. Increasingly over the five years since the first delirium he had avoided people more and more, trusted fewer and became suspicious and retiring. He moved from city to city. He never became clear about the nature of the colorful experience of the first delirium. Eight years later he was still unconvinced of the true nature of his hallucinatory experiences.

Two other patients in this series who experienced shocking hallucinatory and delusional episodes during the dysergastic state were precipitated into a prolonged mental illness. An analysis of the personal history of these patients revealed inadequate management of important life problems.

COMMENT

Variability is the dominant feature of the dysergastic state. Dramatic changes in function occur quickly and reach striking extremes, but like a recurring theme there prevail defects in grasp as well as anxiety and suspicion.

The more acute and severe the dysergastic reaction, from whatever cause, the more it tends toward a dull, semistuperous condition with occasional visual hallucinations. In both such conditions delusional ideas, as might be expected, are extremely fragmentary or absent. Likewise, delusions are practically absent or few and poorly organized in patients during an illness of very short duration and of lesser severity in which dysergastic disturbance amounts to little more than a slight clouding and difficulty in grasp.

Some preservation of the personality and retention of the capacity to form more or less consecutive or related concepts appear essential for the formation of delusions. As a matter of fact, more highly systematized or persistent paranoid misinterpretations did not occur except in illnesses of longer duration and less intensity, e. g., with relatively little clouding of consciousness.

Of the various types of special hallucinations, visual hallucinations occurred most frequently. Tactile and auditory hallucinations were, however, also common, as were combinations of various forms. Olfactory and gustatory hallucinations were less frequently encountered, which was an observation in keeping with general experience.

Interestingly, in the order of their incidence the various types of sensory phenomena that occur in the aura of "epilepsy" parallel those of the dysergastic reaction.[10]

Head[11] described 10 patients who were ill with pulmonary or cardiac disease with pain, often in the presence of fever and prostration, who had a dysergastic reaction. Hallucinations in these patients were dissipated by strong stimulation of the respective end-organs. Thus, olfactory hallucinations, such as the hallucination of hydrogen sulphide, burning earthy odors or gas, disappeared in the presence of

10. Lennox, William G.: The Aura in Epilepsy; a Statistical Review of One Thousand Three Hundred and Fifty-Nine Cases, Arch. Neurol. & Psychiat. **30**:374 (Aug.) 1933.

11. Head, Henry: Certain Mental Changes that Accompany Visceral Disease, Brain **24**:345, 1901.

strong odors. The hallucinatory odor did not blend with the strong odor experimentally introduced, but was actually replaced by it. These observations were confirmed in the patients reported on here. This may be looked on as a further instance of that cardinal feature of the dysergastic state, namely, that patients become more "clear" when specially stimulated, but recede into vagueness and hallucinations when such special external stimulation ceases. The converse was also noted, namely, that factors which induced blurring of perception were those that induced hallucinosis. Analogous observations were made by Liepmann,[12] Bonhoeffer[13] and Hoch,[8] who described hallucinations in delirious patients whose vision was disturbed by producing pressure with the thumb on the eyeball.

Misinterpretations and hallucinations merge and are often hard to distinguish. Mistakes in the identification of common objects are elaborated in various forms of complexity. Some common objects are misconstrued and become a part of the setting of the prevailing delusional belief of the patient, and these misinterpretations are fitted into elaborate plots and persecutions. Others form a part of fleeting or loosely connected dreamlike episodes. Still others are simple mistakes without obvious context, though the error is often on the ominous side. All modalities are involved in such elaborations. Examples have been given to show how physical discomfort during the period of illness may become the starting point of delusional ideas or may become woven into those already present.

Hoch[8] analyzed retention in cases of drug delirium and noted that four figures were the average retained, though seven were occasionally retained, and as few as one was retained by some patients. Tests were made by giving the patient pairs of words to remember for several minutes. Words of habitual association, such as "bread" and "butter," were retained in 57 per cent of trials, and words connected by intimate association, such as "head" and "hair," were retained in 37 per cent, whereas words in no way connected, such as "screen" and "ball," were rarely retained, though the exact figure was not given. Indistinct pictures, such as poor prints, quick flashes of projected images on a ground glass screen (from one-fourth to one-tenth seconds), readily induced misinterpretation and hallucination. In these studies, too, as already noted, similar defects were observed in most patients during some phase of the dysergastic state.

The experiences of the delirious patient—pleasant, unpleasant or neutral—are commonly devoid of personal implications. That is to

12. Liepmann, H.: Ueber die Delirien der Alkoholisten, und über künstlich bei ihnen hervorgerufene Visionen, Arch. f. Psychiat. **27**:172, 1895.

13. Bonhoeffer, K.: Die akuten Geisteskrankheiten der Gewohnheitstrinker: Eine klinische Studie, Jena, Gustav Fischer, 1901.

say, the hallucinatory experiences are seemingly acted on a stage and involve the patient no more than performers acting or the passing of pedestrians on the street. On the other hand, as repeatedly demonstrated in these studies, the content of hallucinations and delusions may be peculiarly individual and to a greater or less extent an expression of the subject's special preoccupations. However, even when the patient is thus deeply implicated the hallucinations and delusions are usually loosely organized and sketchy and though often of fearful dimensions and gruesome vividness are short-lived and discontinuous.

The nature of the dysergastic state is further defined by a consideration of environmental factors which increase the disorder as contrasted with those that help to ameliorate or resolve it. The disturbance is increased by circumstances that call for function of which the patient is barely capable or incapable. This is evidenced chiefly in the difficulty to make fine or even gross discriminations or differentiations. In the realm of vision this defect is brought out by darkness, dim light, half-light, commingled lights and shadows, so that the hallucinatory forms appear under tables, chairs, sheets, pillows, beds and stoves. In the realm of hearing it becomes evident in whispers, distant voices, unclear sounds, great noises (thunder) and unfamiliar noises. In short, new, rapidly changing or complex environmental conditions make the defects in discrimination more apparent.

In contrast, bright, simple, quiet, unchanging, well known surroundings, familiar persons and objects, constant reassurance and repeated explanation and reorientation reduce the disturbance (continuous warm baths exert a similar influence). Thus, an environment which provides the fewest opportunities for false perception is least conducive to dysfunction. In fact, patients function best in a setting which differs little from that to which they are accustomed in ordinary life, or in one neutral in decoration or color. When a patient is in an unfamiliar room he is at least disturbed when it is bright, quiet and simple and when his nurses are seldom changed. A new face may be a disturbing factor, and the time-honored expedient of summoning relatives to the bedside of a delirious patient often does much to restore proper function.

Whether or not there is a specific psychobiologic reaction to any precipitating agent has been a matter of conflicting opinion. Certainly dysfunction at the simplest physiologic level may be vastly different in reaction to various noxious agents and usually affords a ready means of distinguishing one dysergastic reaction from another. Thus, a patient with delirium caused by typhoid fever is readily distinguished from one with delirium caused by pneumonia by virtue of changes in respiration, blood and gastro-intestinal function. Kraepelin postulated however, that by the content of the delirium its etiology could be determined.

This goal has not been attained. Hoch [8] observed that excessive amounts of sedative drugs—morphine, bromides and scopolamine—produce indistinguishable deliria. In comparing his observations with Bonhoeffer's [13] notes on alcoholic deliria, Hoch pointed out that the differences were superficial and of degree rather than of type. Bonhoeffer [1] confirmed Hoch's observation and stated that he had noted no single psychobiologic manifestation of a delirious reaction that could be found to result specifically from one agent and that alone. Krisch [14] later came to the same conclusion, as have other observers who especially investigated the effects of barbital,[1b] bromide [15] and exophthalmic goiter.[16] Moreover, from this study on a still wider variety of patients no evidence was obtained of a specific relationship between any particular noxious agent and the nature of a resulting psychobiologic dysfunction in the dysergastic reaction.

It does not follow from such a statement that the reaction to all agents is the same in all persons or that all dysergastic reactions are identical. Nevertheless, the psychobiologic form and content of the dysergastic reaction is less dependent on the physical or chemical nature of the precipitating agent than on other less precisely definable factors.

Since, then, the precipitating agent bears only a tenuous relationship to the type of the dysergastic reaction, it is relevant to discuss factors which do have a significant bearing on its determination. It is evident from the reports of cases given earlier that in addition to the more nonindividualized defects previously described these patients presented in their reactions peculiarities of form and content which were in good part determined by their personal equipment and experience.[17]

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14. Krisch.[1b c]

15. Karpman, Ben: Bromide Delirium, State Hosp. Quart. **6**:518, 1921; **7**:66, 1921. Diethelm.[1e]

16. Luton, Frank H.: The Rôle of the Thyroid in Mental Illness, read before the Baltimore Society of Neurology and Psychiatry, Feb. 5, 1930.

17. As already mentioned, the reaction to drugs administered in relatively small amounts has not been the subject of this study. However, one aspect of the question should be mentioned. Lewin (Lewin, Louis: Phantastica, Narcotic and Stimulating Drugs, New York, E. P. Dutton & Co., Inc., 1931) described a number of seemingly specific reactions to several drugs, notably Anhalonium Lewinii (mescaline), Cannabis, Agaricus muscarius, Solanaceae, and Banisteria Caapi. But no study of the influence of the environmental setting and individual experience and equipment of the subject on the reaction could be made on the material cited by Lewin. Moreover, many of the reactions described in Lewin's monograph were the expression of acute intoxication, with excitement, overactivity and visual hallucinations. Though no all-inclusive generalization about the action of drugs is justified, the experience gained from this study indicates the need of a searching investigation, in terms of the subject's setting and individual equipment before specificity of reaction can be established.

Even such a common manifestation as fear was to a considerable extent an expression of the habitual reaction to alarming situations. It will be recalled that anxiety, apprehension and fear were present to some extent in every case. It was also clear that those patients who had been known to be most timid, shy or insecure reacted with the greatest show of fear in delirium, and, inversely, those with the greatest feeling of security and fearlessness reacted with the least. No sharp distinction between uneasy apprehension and suspicion could be drawn. In the majority, an uneasy sense of perplexity and doubt or puzzlement was crystallized into a definite paranoid statement or delusional belief. Some doubt and feeling of uncertainty, perplexity, puzzlement, strangeness, isolation, anxiety, mistrust and definite suspicion were invariably present, and the proportions in which these ingredients were mixed were constantly changing. From such a setting the delusional ideas appeared to emerge, but, as in the case of frank fear, the extent and the manner of projecting the cause of such feelings on some influence from without varied directly in proportion to the habitual tendencies of the individual subject.

Analogously, the two patients (cases 7 and 8) who had previously had psychoses which were not dysergastic gave a coloring to their dysergastic states wholly in keeping with their previous psychotic reactions. In other patients (cases 9, 10 and 11) in whom a preexisting personality deviation was complicated by a dysergastic episode the dysergastic state was shaped by the dominant trend.

In still other patients who were observed during different dysergastic states, whether the etiologic agent was the same or quite different on successive admissions, the dysergastic reactions bore a striking resemblance—in some cases, even down to minor details (cases 1 and 6). Such similarities could best be explained in terms of the subject's individual equipment and experience.

Age, sex and intellectual endowments are directly reflected in the content. Men show a greater interest in business concerns and careers and women in moral character and in children. Men seldom believe themselves accused of leading an immoral sex life, with the exception of perversion, whereas a considerable number of women do. Primitive formulations and reactions were common in children and mental defectives, whereas the delirious content of sophisticated persons was commensurate with their intellectual development.

Patients with well marked individual characteristics preserved such characteristics, which shaped much of the clinical picture. The bombastic, the pathologically suspicious and the patients with obsessional trends showed these tendencies in more intensified form or almost in caricature.

Similarly, major interests were clearly defined. Preoccupation with religion or work and past experiences of high individual value to the patient, whether recent or remote, also played their part. General life situations, especially those involving marital and important human relations, became woven into the pattern of the reaction.

These observations are in keeping with the experience of other investigators. The influence of the subject's dominant mood on the content of the dysergastic reaction has been described by Bonhoeffer.[18] He observed a woman who had previously had frank manic attacks and who became delirious as an accompaniment of heart failure with aortic insufficiency and stenosis. The delirium was characterized by flight of ideas, distractibility and elevation of mood, interspersed with numerous hallucinatory voices that criticized and scolded.

Haviland[7] described 10 cases of delirium with infection. Two patients characterized as overactive, talkative and funny were in health "giddy and wild" or happy, energetic and outgoing. Krisch[19] described a readily frightened young woman in whom there developed delirium (mastitis) characterized by stupor and other features of a mood disturbance. Some years later she experienced a pure affective disorder (manic) without associated infection. Another patient,[20] a woman of happy, outgoing, joyous type, though readily overcome by sadness, had delirium associated with sepsis following a criminal abortion. The dysergastic state was characterized by flight of ideas, push of speech and hypermotility.

Akin to patients with dominant moods in the dysergastic reaction are those previously described in whom delirium develops during an already existing psychopathic state. Usually, because of their depression, restlessness, anxiety or sleeplessness, the patients took sedative drugs in excessive amounts. Jameison and Wall[21] described 4 such patients. In their case 1, a woman, several members of whose family had had affective psychoses, 2 of whom had committed suicide, had an attack of excitement followed by depression. She took sedatives in excess to relieve the distress, and a drug delirium developed. Her dominant mood was depression; several suicidal attempts were made, and she repeatedly begged to be allowed to die. Case 2 was that of a man who had severe depression after business reverses. This was followed by excitement, for which he took sedatives. Delirium developed in which excitement and overactivity dominated. In case 3 the patient was in a paranoid state and took bromides in excess for

18. Bonhoeffer,[1a] p. 94.

19. Krisch,[1c] p. 83.

20. Krisch,[1c] p. 87.

21. Jameison, G., and Wall, J. H.: Toxic States as Complications in Functional Psychoses: Etiology and Treatment, Psychiat. Quart. **4**:263 (April) 1930.

relief from the constant annoyance of "persecutions." The drug delirium that followed was shaped by preexisting notions. The patient in case 4 was an alert and practical but sensitive, reserved and stubborn woman, who worried a great deal. She experienced a postpartum psychosis, during which she was tense, agitated and apprehensive. She was given sedatives. She became inaccessible, negativistic and mute and repeatedly expressed ideas about the death of her husband and baby. In the published reports of cases, as well as in those we have presented, the resultant dysergastic state was colored strongly by the underlying mood or thinking trends. The course of the illness was prolonged and the date of termination was difficult to define.

Others have observed dysergastic patients in more than one delirious episode. Thus, Krisch [22] described a patient who was observed during two separate periods of delirium. She was slightly feebleminded and had mastitis on first admission and bronchopneumonia on the second. The deliria during the two illnesses were similar and were characterized by anxiety, push of speech and excessive motility. A second patient [1b] (case 10) suffered from delirium on two occasions as an accompaniment of chronic nephropathy. The patient was described as having been a child of "silent, shy nature, never energetic, boisterous or joyous." As a young adult he was refused for military service because of general disability. The two delirious episodes resembled each other. He was anxious and often fearful and felt himself pursued by persons who sought his life. He was depressed and talked of suicide.

Dominant preoccupations coloring the dysergastic reaction have also been described. Thus, Karpman [15] described a patient (case 3) with homosexual yearnings who suffered from bromide delirium. The fear of losing the love object and the fantasy of homosexual fulfilments were vividly expressed in the delirium.

Patients in actual delirium are not to be sharply distinguished from those in whom hallucinations predominate and in whom some special topic or preoccupation is outstanding. Thus, Kirby [23] in 102 cases of alcoholic hallucination found in every case in which the personality of the patient could be more fully investigated that serious maladjustment preceded the expression of systematized delusions during the alcoholic state. He concluded that the topics of major interest and the accompanying hallucinosis were not specifically of alcoholic origin but were dependent on individual conflicts in the presence of alcoholic excesses.

Conflicts which in normal waking states present no pathologic proportion are often given frank expression in the dysergastic state. This

22. Krisch,[1c] p. 57.

23. Kirby, George H.: Alcoholic Hallucinosis, with Special Reference to Prognosis and Relation to Other Psychoses, Psychiat. Bull. **1**:353, 1916.

was demonstrated by the 2 patients (cases 13 and 14) who engaged in obsessive hand-washing. Again, in childless women there was preoccupation about children and bearing of children, expressing itself in 1 as a delusion of having "many babies" (case 7) and in another in the erroneous belief that she had given birth to twins (case 18).

Recall is usually good, and the patient frequently describes his experiences as "dreamlike" or like a "nightmare." Clear memory of many of the hallucinatory experiences is the rule.

Insight is occasionally present even during the period of illness, but generally is absent. But insight, like other features of the dysergastic state, varies from time to time and occasionally with great rapidity. Thus, patients tell of hallucinatory experiences in a detached manner, only to be embroiled in the assault of hallucinatory figures shortly after.

Insight, to be sure, is related to outcome and seems to be in part dependent on the significance of the dysergastic experience to the patient. Episodes of minor importance are, with the subsidence of the effects of the noxious agent, quickly appreciated and dealt with in a detached, objective manner. On the other hand, especially in those with deeply ingrained feelings of distrust and insecurity, delusional and hallucinatory episodes of grave personal significance or involving strong social taboos are less well managed, and sometimes patients after the reestablishment of comparatively normal health retain isolated bits of poorly digested experience centered about potent and improperly evaluated delirious episodes. In case 20 the content of the delirious hallucinatory experience was dominated by the patient's sexual preoccupations. The fact that the hallucinatory and delusional content was so significant for him seemed to have interfered with the development of a detached view about his experience. Others are precipitated into prolonged illness with ominous manifestations. The feebleminded, too, often lack complete objectivity and detachment for the episodes of the delirium for indefinite periods.

Thus, the duration of the illness and its prognosis in a patient in the dysergastic state are determined not alone by the severity and duration of the source of the noxious agent but to some extent by the state of mental health before the onset of the illness and the reaction of the patient to episodes that occurred during his delirious state.

In the vast majority of instances in this study the disturbance dissipated within a month, though occasionally several months were necessary and occasionally a typical dysergastic reaction slowly metamorphosed into a prolonged illness which bore only traces of the original dysergastic form and took on more and more the coloring of a severe disorganization of personality. Moreover, the danger to life in the dysergastic state is not only from the direct effect of the noxious agents but from the prostration that follows extreme restlessness, especially in those with failing circulation.

FORMULATION

Classification of the total activity of subjects in the dysergastic state into two such categories as "physical" and "mental" is an oversimplification. In fact, rather than clarifying issues, this useless dualism with its implied antithesis actually creates a dilemma. It is an idle and profitless exercise to discuss whether shadows, loud noises, failure in visual accommodation or tinnitus produced "physiogenetically" or "psychogenetically" their effects in the cases reported here. It is, however, desirable to formulate data in a manner which allows expression of the facts and which does not create divisions nonexistent in nature and for which there is no pragmatic sanction.

Meyer has had recourse to the concept of levels of integration, referring for purposes of general orientation to the simplest levels as the physiologic and the more complex as the psychobiologic. Such a point of view replaces the oversimple dualism of "physical" and "mental" by creating a pluralism of many levels or stages of complexity ranging from the integrated action of a few cells of unitary function to the integration of different complex functional units. In this hierarchy are included both the simple chemical or humoral integration, such as that in smooth muscle and gland, and that of the various levels of anatomic complexity of the nervous system with every accompanying variety of functional elaboration.

In the dysergastic reaction many integrative levels are impaired. Thus, at the simplest physiologic level there are such defects as constipation, vasodilatation, circulatory impairment and edema; at a relatively simple neural integrative level, defects such as tremor and alterations in tendon reflexes; at a more elaborate, yet still relatively simple neural level, sensory and motor defects shown in hallucinations and restlessness and in the realm of the most complex level, defects in judgment and individualized delusions of a relatively systematized order.

Hence it is apparent that the dysergastic reactions include several levels and that a consideration of a patient from the simple levels alone is incomplete if not misleading. This working plan does not belong to the category of metaphysics but has to do with the simple, direct manipulation of the facts of human behavior.

SUMMARY

In a series of 106 patients in whom the dysergastic reaction was precipitated by twenty-seven different noxious agents, no evidence was found that there was any specific relationship between a particular noxious agent and the form and content of the accompanying psychobiologic disturbances.

Variability was the dominant feature of the dysergastic reaction. Defects in grasp, failure in sustained mentation, fear or anxiety, suspicion, misinterpretation, hallucinosis and restlessness were its prevailing manifestations. The dysfunction was usually worse at night, during the latter part of the day, with attempts at sustained effort, and immediately after awakening. Furthermore, the defects were aggravated by new, rapidly changing, complex environmental conditions or by situations that demanded discrimination of which the patient was incapable. In contrast, simple, neutral, familiar and readily resolvable environmental situations minimized the disturbance.

The psychobiologic content of the dysergastic state was shown to be in large part dependent on the individual equipment and experience of the subject. Patients during repeated dysergastic reactions induced by different agents presented in each of their several periods of illness recurring and readily recognizable individual features. Also, subjects who had had affective psychoses earlier in life exhibited during the dysergastic state disorders of mood akin to those of their other psychotic reactions. Distinctive personal characteristics, habits of reaction, dominant interests, past experiences, age, sex and intellectual endowment unmistakably molded and individualized the resultant reaction to any noxious agent.

Paranoid misinterpretations were common in the dysergastic state, though systematization seldom occurred except when the dysfunction was of prolonged duration and of relatively slight intensity. This was particularly true in subjects who were known to have been inordinately suspicious.

The course of the dysfunction was usually short-lived, though the outcome was dependent not alone on the elimination of the noxious agent but also on the adjustment of the subject's personality before the onset of the dysergastic state. It was dependent as well on the significance to the patient of his experiences during the dysergasia and consequently his reaction to the delusional and hallucinatory episodes of his illness.

Though the nature of the noxious precipitating agent is a factor in determining dysfunction at the physiologic level, the course and manifestations of the dysergastic reaction at the psychobiologic level are primarily determined by (1) the intensity and duration of the functional disturbance, (2) the environmental stimuli during the period of the illness and (3) the individual equipment and experience of the subject.

DEMENTIA PARALYTICA

RESULTS OF TREATMENT WITH TRYPARSAMIDE

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BOSTON

Ten years have elapsed since the introduction of tryparsamide in the treatment of neurosyphilis. After the communication of Lorenz and his associates [1] in 1923, the drug was given further trial in various clinics throughout the country. In the course of these ten years a number of reports on the use of tryparsamide as a therapeutic agent in cases of neurosyphilis have appeared, and almost without exception the reports have been favorable. The popularity of tryparsamide may have been overshadowed by the more extensive literature from all parts of the world on malarial treatment of dementia paralytica. While the American literature contains many reports on treatment with tryparsamide, the foreign literature is particularly lacking in reports on the subject. Lichtenstein [2] gave a complete bibliography on the subject up to 1931 and emphasized that tryparsamide is still used relatively little in the treatment of neurosyphilis. Therefore, it seems justifiable to present the results of the use of tryparsamide in the treatment of dementia paralytica at the Boston Psychopathic Hospital, where the drug has been used since 1923.

In a recent book, Moore [3] stressed the value of tryparsamide in the treatment of meningovascular types of neurosyphilis but stated that fever therapy is the method of choice in the treatment of dementia paralytica. However, in the same chapter he said that remissions occur in about 30 per cent of patients with dementia paralytica treated with tryparsamide. A complete list of the reports in the literature is contained in Moore's bibliography. Some of the earlier favorable reports,

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Read at a meeting of the Boston Society of Psychiatry and Neurology, Nov. 15, 1934.

From the Boston Psychopathic Hospital and the Department of Psychiatry, Harvard Medical School.

1. Lorenz, W. F.; Loevenhart, A. S.; Bleckwenn, W. J., and Hodges, E. J.: The Therapeutic Use of Tryparsamide in Neurosyphilis, J. A. M. A. **80**:1497 (May 26) 1923.

2. Lichtenstein, Julia: Follow-Up of Seventy-Six Patients with Neurosyphilis Treated with Tryparsamide, Arch. Dermat. & Syph. **24**:182 (Aug.) 1931.

3. Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

besides the original communication of Lorenz,[1] are those of Stokes and Wilhelm,[4] Moore and Robinson,[5] O'Leary and Becker,[6] Solomon and Viets,[7] Schwab and Cady [8] and Kirby and Hinsie.[9] These reports deal with varying numbers of patients and demonstrate a relatively high degree of therapeutic efficiency of tryparsamide in the treatment of neurosyphilis. The percentage of cases of all types of neurosyphilis in which improvement was obtained varied from 30 to 66.6. In cases of dementia paralytica the figures were lower, but in early cases an incidence of remission of about 30 per cent was noted by most authors.

O'Leary and Becker, in 1926, published observations on 152 cases at the Mayo Clinic previously reported by Stokes and Wilhelm, but they eliminated 40 advanced cases of dementia paralytica and added 75 cases which had been under observation since 1924. They reported that there was marked improvement in 12 per cent of the cases of dementia paralytica, improvement in 66 per cent and no improvement in 22 per cent. In a second report by Kirby and Hinsie,[10] published in 1929, a survey of the status of 67 patients with dementia paralytica who had been treated with tryparsamide showed that 28 per cent obtained a complete remission, 26 per cent were improved, 12 per cent were unimproved and 34 per cent died. Another follow-up report was published in 1928 by Lorenz [11] and his co-workers. Of the 152 patients suffering from dementia paralytica who were treated with tryparsamide, 134 remained well for from five to six years, 4 died and 14 returned to state hospitals. In this series the patients with the expansive type of the disease responded best. However, even in those showing less improvement the general condition improved, and in nearly every case there was an increase in body weight and strength. Menzies,[12] in a

4. Stokes, J. H., and Wilhelm, L. F. X.: Tryparsamide in the Treatment of Neurosyphilis, Arch. Dermat. & Syph. **11**:579 (May) 1925.

5. Moore, J. E., and Robinson, H. M.: Results of Tryparsamide Therapy in Syphilis, J. A. M. A. **83**:888 (Sept. 20) 1924.

6. O'Leary, P. A., and Becker, S. W.: Further Observations on the Treatment of Neurosyphilis with Tryparsamide, M. J. & Rec. **123**:305 (March 3) 1926.

7. Solomon, H. C., and Viets, H.: Comparison of Tryparsamide in Treatment of Neurosyphilis, J. A. M. A. **83**:891 (Sept. 20) 1924; Tryparsamide Treatment of Neurosyphilis: Second Report, ibid. **85**:329 (Aug. 1) 1925.

8. Schwab, S. L., and Cady, L. D.: Tryparsamide and Syphilis of the Nervous System (Preliminary Report), Arch. Neurol. & Psychiat. **13**:80 (Jan.) 1925.

9. Kirby, G. H., and Hinsie, L. E.: Tryparsamide Treatment of General Paresis, State Hosp. Quart. **12**:53 (Nov.) 1926.

10. Kirby, G. H., and Hinsie, L. E.: Psychiat. Quart. **3**:68 (Jan.) 1928.

11. Lorenz, W. F.: Late Results from Tryparsamide Therapy in Neurosyphilis, J. A. M. A. **90**:1285 (April 28) 1928.

12. Menzies, E. C.: A Review of the Progress and Results in Forty-One Cases of Paresis and Taboparesis Treated with Tryparsamide, Canad. M. A. J. **20**:242 (March) 1929.

review of the progress and results of treatment with tryparsamide in 41 cases of dementia paralytica and the tabetic form of dementia paralytica, reported that 10 patients had had remission for at least four years, that 14 were living, with varying degrees of mental defect, and that 17 had died.

MATERIAL AND METHOD OF ANALYSIS

This report deals with the cases of 81 patients with dementia paralytica to whom more than ten injections of tryparsamide were administered between June 1923 and June 1930 at the Boston Psychopathic Hospital and in the private practice of one of us (H. C. S.). There is an analysis of the results of this treatment in the year 1933. Three of the patients had received fewer than 15 injections of tryparsamide, whereas 3 others received 269, 262 and 254 injections, respectively. As will be shown later, some patients in the series received other treatment prior to that with tryparsamide, but the common factor in the treatment of all the patients was tryparsamide. This group of cases and the results obtained are therefore not exactly comparable with series reported by other authors. As in the reports on malarial treatment, there are hardly two groups of cases in the literature that are comparable with one another, as so many variants enter into consideration, for example, of the exact type and amount of treatment, the selection of patients and the length of time that the patients were followed up before the report was made.

One reason for reporting on this series of cases is that the patients have been carefully followed over a period of years and the results represent a moderately exact summary of what has been accomplished in a reasonably large group. The period of observation after the onset of symptoms of dementia paralytica in these cases varied from a minimum of three years to a maximum of fifteen years.

In each case the diagnosis was made on the basis of clinical studies and observations on the spinal fluid, it being held requisite for a diagnosis that the spinal fluid give the typical strong reaction characteristic of the disease. No patient had a normal fluid before tryparsamide was administered and the fluid of only 8 patients gave a moderately positive or weakly positive reaction as a result of other treatment prior to the introduction of tryparsamide therapy.

We wish to emphasize that this material is somewhat selective. Many of the patients were ambulatory and presented a rather early stage of the disease. Moreover, because of limited bed space a selection of patients entering the hospital was necessary, so that, on the whole, those in whom the disease was in the earlier periods and who were in fairly good condition were chosen. It must also be noted that some patients had had a considerable amount of treatment prior to 1923. Tryparsamide was given to these patients after other treatment either because they were not progressing satisfactorily from the clinical or from the serologic standpoint or because they were anxious to secure the benefit of the new drug. The duration of symptoms of dementia paralytica prior to the use of tryparsamide varied from two months to four years.

The results of treatment are analyzed from two points of view: (1) the clinical status of the patient and (2) the observations on the spinal fluid. While we recognize the difficulties encountered in evaluating the clinical results in cases of dementia paralytica, we have attempted to make such an analysis. For classification we have used the following groups: 1. Patients who had made an improvement sufficient to allow them to take their places in the community and to return

to work we designated as showing "arrest" of the disease. These patients are comparable to those described in the literature as having "complete remission" or "full remission." 2. Patients who had shown some improvement and had maintained a stationary level of efficiency, with from a moderate to a marked degree of mental defect, we placed in a second group, calling their condition "stationary." In this group were many hospitalized patients who might be considered in the group with partial remission. 3. The status of patients who had shown little or no improvement, most of whom were living in state hospitals, has been considered as "unimproved."

TABLE 1.—*Clinical Status of Patients with Dementia Paralytica*

Total Number of Patients Treated	Condition					
	Arrested		Stationary		Unimproved	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
81	34	42.0	24	29.6	23	28.4

TABLE 2.—*Analysis of Cases of Fourteen Patients Who Died After Treatment with Tryparsamide*

Patient	Clinical Status Before Death	Condition of Spinal Fluid Before Death	Cause of Death	Duration of the Disease
J. L. P.	Unimproved	Unimproved	Seizures	2 years
F. G.	Unimproved	Unimproved	Sepsis	2 years
A. F.*	Stationary	Normal	Cerebral hemorrhage	3½ years
T. W.*	Stationary	Moderately improved	Brain abscess	4 years
J. S.*	Stationary	Normal	Cardiac failure	4 years
S. D.	Unimproved	Unimproved	Dementia paralytica	5 years
B. M.*	Stationary	Unimproved	Bronchopneumonia	5 years
C. P.	Unimproved	Unimproved	Cellulitis	6 years
S. P.	Unimproved	Unimproved	Dementia paralytica	7 years
E. B.*	Arrested	Normal	Cerebral hemorrhage	7½ years
L. G.*	Stationary	Normal	Septicemia	9 years
A. S.*	Stationary	Moderately improved	Paretic seizures	10 years
E. D.*	Stationary	Normal	Dementia paralytica	10 years
G. P.*	Stationary	Normal	Pyelonephritis	15 years

* This patient was considered to be clinically improved; the cause of death is indicated.

RESULTS

In table 1, we present an analysis of the clinical status of the entire group in 1933. According to our analysis, in 42 per cent of the 81 patients the condition was arrested in June 1933, and in nearly 30 per cent it was stationary, with some degree of mental defect. The remaining 28 per cent showed no improvement.

Table 2 shows an analysis of the deaths in the series. It will be seen that the expectation of life is greatly increased, since the average duration of life of the untreated patient with dementia paralytica is considered to be two and a half years after the onset of symptoms. Of the 14 deaths, 5 were considered to be due to the disease itself, and

in these patients no improvement was noted as regards either the clinical status or the response of the spinal fluid. Death occurred in 8 cases in which a stationary level had been maintained for from three and a half to fifteen years. In only 2 of these was the disease itself considered to be the cause of death, and in both death occurred ten years after the onset of the disease. In the other cases death was due to various conditions, including cerebral hemorrhage, cerebral abscess, general septicemia, cellulitis, bronchopneumonia and pyelonephritis. The spinal fluid was normal in 6 cases prior to death. In 1 case in which the condition was apparently completely arrested and in which the reaction of the spinal fluid was negative, the patient died seven and a half years after the onset of dementia paralytica as a result of a cerebrovascular accident.

In table 3 we present the observations on the cerebrospinal fluid. A completely normal fluid was obtained in 37.5 per cent of the cases; in an additional 16.3 per cent the condition of the fluid was markedly

TABLE 3.—*Condition of Spinal Fluid of Patients with Dementia Paralytica in 1933*

Total Number of Patients Treated	Spinal Fluid							
	Normal		Greatly Improved		Moderately Improved		Unimproved	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
80*	30	37.5	13	16.3	8	10.0	29	36.2

* In 1 case the final result was not available.

improved. In 10 per cent it showed moderate improvement, and in 36.2 per cent it was considered as unimproved. By a "completely normal" fluid is meant a fluid showing a cell count under 5, a negative reaction for globulin, a total protein content under 40 mg. per hundred cubic centimeters, a negative reaction of the colloidal gold test and a negative Wassermann reaction with 1 cc. of fluid. A "greatly improved" fluid was one in which the reactions were very weak, approaching but not quite negative, whereas a "moderately improved" fluid showed a reasonable reduction from the original strongly positive formula.

With regard to the effect of tryparsamide on the spinal fluid in dementia paralytica, Bunker [13] stated: "Consistent results were scarcely obtained with fewer than eighty injections of tryparsamide of 3 Gm. each." With this opinion we are in accord, and we would emphasize that the attainment of negative serologic reactions as a rule requires the administration of many more injections than are apparently necessary for a favorable clinical result. At the same time, we agree with many other workers that if a clinical arrest is to be obtained it will

13. Bunker, H. A.: Effect of 100 Injections of Tryparsamide upon the Spinal Fluid in General Paresis, Am. J. M. Sc. **175**:265 (Feb.) 1928.

occur generally by the time from forty to fifty doses have been given. This does not apply to the serologic tests, however, as these usually become negative eventually if the administration of tryparsamide is continued for a sufficiently long period, far beyond the point of clinical remission. In fact, we have previously stated [14] that with the persistent use of tryparsamide negative serologic reactions are generally, though not invariably, secured. We have also pointed out that there is no complete parallelism between the clinical results and the observations on the spinal fluid. Nevertheless, significant information is obtained from following the course of the response of the spinal fluid to treatment, and it is our opinion that a completely normal spinal fluid is a good indication of the arrest of the activity of the disease. Even though the disease process is arrested, the clinical results may be poor because of the damage to the parenchymatous tissue which had occurred previously.

TABLE 4.—*Relationship Between the Clinical Condition and the Response of the Spinal Fluid*

Number of Patients	Clinical Status	Condition of Spinal Fluid				
		Normal	Greatly Improved	Moderately Improved	Unimproved	No Test
34	Arrested	20	8	5	1	..
24	Stationary	10	4	3	7	..
23	Unimproved	0	1	0	21	1
81	Total.....	30	13	8	29	1

In this connection, table 4 reveals the striking phenomenon that none of the patients who clinically were unimproved had a normal spinal fluid, and in all but 1 the fluid showed no improvement. This table gives an analysis of the relationship between the clinical and the serologic results in our series. From this analysis one can conclude that there is a definite relationship between the clinical status and the reaction of the spinal fluid, at least so far as the group which showed no improvement is concerned. With regard to the patients in whom the disease was arrested, it will be seen that of the 34 patients, 28, or slightly more than 80 per cent, had completely normal or nearly normal spinal fluid. In the group in which the condition was stationary the correlation is not close, only 10 of the 24 patients showing completely normal fluid. The same type of correlation between the clinical and the serologic results may be seen in table 5, which gives an analysis of 64 of the 81 cases in which the patient received tryparsamide alone with no other treatment prior to or subsequent to the administration of this drug.

14. Solomon, H. C., and Epstein, S. H.: Tryparsamide in the Treatment of Neurosyphilis, New York State J. Med. **31**:1012 (Aug. 15) 1931.

By way of contrast, it may be mentioned that in our series of patients treated with malaria previously reported on [15] there was little in the way of definite correlation between the clinical status and the serologic results, even though tryparsamide was given to many patients after the course of malarial treatment. Of the 24 patients who were clinically unimproved after malarial therapy, 12 had normal spinal fluid. This, we believe, was due largely to the fact that the great majority of patients treated with malaria who live for any length of time after

TABLE 5.—*Status of Sixty-Four Patients Treated with Tryparsamide Alone*

Number of Patients	Clinical Status	Condition of Spinal Fluid				
		Normal	Greatly Improved	Moderately Improved	Unimproved	No Test
24	Arrested	11	7	5	1	..
18	Stationary	7	2	2	7	..
22	Unimproved	0	1	0	20	1
64	Total	18	10	7	28	1

TABLE 6.—*Record for Eighteen Patients Treated with Tryparsamide Alone Whose Spinal Fluid Became Normal*

Patient	Number of Injections of Tryparsamide	Time From Onset of Treatment, Years
L. T.	20	1
C. F.	25	1
P. C.	35	1
J. G.	40	2
A. M.	60	2
J. S.	65	2
T. S.	73	2
M. J.	88	3
A. O.	27	3
D. O.	121	3
A. G.	54	4
M. P.	72	4
P. S.	93	4
F. S.	230	7
L. G.	31	8
J. F.	56	8
A. C.	87	8
E. D.	23	9

treatment show considerable improvement in the spinal fluid regardless of the clinical status. The time element, therefore, plays an important rôle in the changes in the spinal fluid; e. g., within the first year after malarial treatment the number of cases in which one finds marked improvement in the spinal fluid is much less than that found if the patients are examined again at the end of several years. Likewise, in our patients who received tryparsamide the effect of time in bringing about normality of the spinal fluid was important. Table 6 indicates

15. Solomon, H. C., and Epstein, S. H.: Dementia Paralytica: Results of Treatment with Malaria in Association with Other Forms of Therapy, Arch. Neurol. & Psychiat. **33**:1008 (May) 1935

that as the years go by more and more patients show normal cerebrospinal fluid. Of the 64 patients who received tryparsamide alone, 18 showed normal spinal fluid. In 1 case the fluid did not become normal until nine years after treatment with tryparsamide was started; in 3 cases it was eight years before this result was obtained, and in 1 case treatment was continued for seven years before the spinal fluid became normal, whereas in only 3 cases did the fluid become completely normal in one year. In 7 of the 18 cases in which the spinal fluid became normal the result was obtained in two years or less, whereas in the other 11 cases more than two years were required to obtain this result. It may also be pointed out that in 24 of the cases in which the spinal fluid did not become normal the period of observation of the spinal fluid subsequent to the beginning of tryparsamide therapy was less than three years.

In cases in which other types of antisyphilitic treatment were administered prior to the introduction of tryparsamide therapy the effect of time on the spinal fluid was similar. Seventeen patients in the series received other treatment besides tryparsamide; in 12 the spinal fluid became completely normal. Table 7 indicates the treatment received by these 12 patients and the time required in each instance to bring the fluid to a normal state. Only 1 patient had normal spinal fluid in as short a time as two years; 3 patients had normal fluid after three years had elapsed, and the remaining 8 patients required four years or more before a negative result was obtained. In 1 instance the spinal fluid did not become completely normal until after thirteen years of treatment. The table also indicates that the quantity of tryparsamide given was in most cases more than 40 injections. To 3 of the patients, 154, 134, and 123 injections, respectively, were given. It has been shown in a previous communication on malarial treatment of dementia paralytica [15] that patients who had not done well after the administration of considerable amounts of the arsphenamine preparations, bismuth and mercury, and after intraspinal and intracisternal injections and spinal drainage, showed a prompt favorable response after malarial treatment. The same may be said to be true after the administration of tryparsamide to patients who had not done well under the other forms of antisyphilitic therapy. In any case, it is apparent in our series that the spinal fluid showed considerable improvement in most instances.

As already mentioned, we are dealing not only with the effect of time on the changes in the spinal fluid but with the effect of the amount of tryparsamide given in an individual case. That dosage plays an important rôle in the effect on the spinal fluid has been stressed by other authors. This is illustrated in our series by the example mentioned in which seven years elapsed before a normal spinal fluid

was obtained; in this case 230 injections of tryparsamide were used during the seven year period. We have already emphasized our belief that frequently more than 40 or 50 injections, usually considered sufficient for a good clinical result, are necessary in order to obtain normality of the spinal fluid. This opinion is borne out by the data in tables 6 and 7, indicating that the majority of patients with normal spinal fluid received more than 50 injections of tryparsamide. It is also evident

TABLE 7.—*Twelve Patients Treated with Tryparsamide in Association with Other Forms of Therapy Whose Spinal Fluid Became Normal*

Patient	Time From Onset of Treatment, Years	No. of Injections of Tryparsamide	No. of Injections of Arsphenamine	No. of Intradural Injections	No. of Injections of Mercury	No. of Injections of Bismuth
G. P.	2	56	65	8 intraspinal	20	..
A. F.*	3	87	23	11 intraspinal; spinal drainage 9 times	..	..
J. H.†	3	8	..	6 intraspinal	..	25
R. L.*	3	42	33	6 intraspinal; 22 intracisternal; spinal drainage 6 times	..	..
F. C.	4	134	24	6 intraspinal	17	..
E. B.*	4	52	..	13 intraspinal; 7 intraventricular; spinal drainage 35 times	66	..
J. W.*	4	15	21	2 intraspinal	..	..
A. G.*	6	20	40	5 intraventricular	..	..
J. H.	6	154	15	.....	36	..
H. B.	9	123	8	8 intraspinal; spinal drainage 8 times	22	..
A. F.*	9	23	15	22 intraspinal; 3 intracisternal; spinal drainage 15 times	46	..
J. H.*	13	77	118	4 intraspinal	8	..

* This patient showed moderate improvement of the spinal fluid prior to treatment with tryparsamide.

† Amblyopia developed in this patient; the administration of tryparsamide was discontinued and a series of diathermy treatments was substituted.

that there are exceptions on both sides, some patients having normal fluids after very little treatment while in others the fluid does not respond favorably even after prolonged treatment.

The superiority of tryparsamide and malarial treatment was clearly shown by Hopkins [16] in a review of the results of treatment in 680 cases of neurosyphilis. One hundred and fifty-three cases of dementia paralytica were considered in this report, and various types of treatment,

16. Hopkins, H. H.: Treatment of Neurosyphilis: Review of Results in Six Hundred and Eighty Patients, Arch. Int. Med. **52**:66 (July) 1933.

classified according to the methods of the Johns Hopkins Clinic,[17] were employed. Sixty-five of the patients received so-called "poor treatment" and "routine treatment." Of these, 10.5 per cent were considered to show good remission, 6 per cent showed fair results, 12 per cent showed poor clinical results, 54 per cent died of the disease and the remaining 17 per cent died of causes unknown. Thirty-five patients received "routine treatment plus tryparsamide," and a few of these received intraspinal therapy. Good remission occurred in 31 per cent of these patients, results considered as fair in about 6 per cent and poor results in 17 per cent; 46 per cent died. About 6 per cent of the deaths were from unknown causes. The condition of the spinal fluid in this group was excellent in 40 per cent, fair in 6 per cent, poor in 37 per cent and unknown in 17 per cent. The third group consisted of 53 patients who received "routine treatment plus malarial," and of these 54 per cent had a good remission, 5 per cent showed fair results, 22 per cent showed poor clinical results, 17 per cent died of syphilitic disease, and 1 per cent died of unknown causes. The condition of the spinal fluid was excellent in 26 per cent, fair in 37 per cent, poor in 9 per cent and unknown in 28 per cent.

Of our 81 patients, 17 received fever treatment after a considerable amount of tryparsamide had been given without leading to improvement. The end-results in these patients are analyzed in table 8. Fifteen had received malarial therapy; 1 had received treatment with rat-bite fever, and 1 had received injections of typhoid vaccine. Following fever treatment, 16 of the patients who had showed little or no appreciable improvement after receiving a considerable amount of tryparsamide were clinically improved, and 15 of them showed marked improvement in the spinal fluid. We consider these results to be noteworthy. They are much better than would be expected in a series of patients treated by malaria alone, and they are certainly better than those obtained by us in any other group or than those obtained in any group reported in the literature. From the laboratory standpoint alone

17. "Poor treatment" consisted of less than one year of treatment with arsphenamine and heavy metals and, in a few cases, with tryparsamide. "Routine treatment" consisted of courses of from 6 to 8 injections of the arsphenamine products (arsphenamine, neoarsphenamine and silver arsphenamine) alternating with courses of treatment with mercury or bismuth, or both, together with potassum iodide for at least a year. Routine treatment to which was added a variable number of intraspinal treatments at intervals of at least two weeks was the third method used in the clinic. "Routine treatment plus tryparsamide" consisted of courses of from 10 to 20 injections of tryparsamide, alternating with courses of treatment with bismuth or mercury and, in some instances, the arsphenamines. "Routine treatment plus malaria" included treatment with tryparsamide either before or after malarial therapy.

they represent a striking example of therapeutic success. We cannot agree with some authors, notably Kirby and Hinsie,[10] who have expressed the belief that malarial treatment is ineffective when given to patients who have had considerable amounts of tryparsamide. In fact, they stated that in many instances the spinal fluid showed reversal from a weak or moderately positive reaction to a strongly positive reaction after fever therapy. In our experience this has occurred in no case; in fact, improvement in the fluid is the rule. In these cases it seems that fever is the potent factor in reducing to normal spinal fluid that has been apparently resistant to the effects of tryparsamide. In

TABLE 8.—*Results of Subsequent Fever Therapy in Seventeen Patients*

Patient	Clinical Status Prior to Fever Therapy	Condition of Spinal Fluid Prior to Fever Therapy	Type of Fever	Results	
				Clinical Status	Condition of Spinal Fluid
B. A.	Unimproved	Unimproved	Malaria	Stationary	Normal
H. L.	Stationary	Unimproved	Malaria	Arrested	Normal
F. A.	Unimproved	Unimproved	Malaria	Stationary	Normal
M. T.	Unimproved	Unimproved	Malaria	Arrested	Normal
J. L.	Unimproved	Unimproved	Malaria	Stationary	Normal
S. G.	Unimproved	Unimproved	Malaria	Stationary	Normal
B. E.	Unimproved	Unimproved	Malaria	Arrested	Normal
A. V.	Unimproved	Unimproved	Malaria	Stationary	Greatly improved
K. B.	Unimproved	Unimproved	Malaria	Arrested	Normal
R. D.	Unimproved	Unimproved	Malaria	Arrested	Greatly improved
F. W.	Unimproved	Unimproved	Malaria	Arrested	Normal
C. D.	Unimproved	Unimproved	Malaria	Arrested	Moderately improved
H. F.	Unimproved	Unimproved	Typhoid vaccine	Arrested	Greatly improved
D. R.	Unimproved	Unimproved	Malaria	Arrested	Moderately improved
E. C.	Unimproved	Unimproved	Malaria	Stationary	Normal
D. S.	Stationary	Moderately improved	Malaria	Arrested	Normal
A. S.*	Stationary	Moderately improved	Rat-bite fever	No change	Normal

* This patient died ten years after the onset of dementia paralytica and four years after the fever treatment, the spinal fluid having become normal.

this respect there is a direct analogy to the superiority of tryparsamide to arsphenamine and bismuth for treatment of neurosyphilis. It is our opinion that time alone is not the sole factor in producing this improvement, because in many instances in this series the administration of tryparsamide was continued for four years before malarial therapy was instituted. It is fair to assume that the addition of malaria or tryparsamide in the prolonged regimen serves as a turning point toward the final success of treatment. The mechanism of action in these cases is by no means clear. However, we have had enough experience to convince us that patients who are not doing well while receiving tryparsamide alone may still show marked improvement following fever therapy.

If the figures for the results of treatment with tryparsamide in our series of 81 cases are altered to include the results subsequent to fever therapy in these 17 patients (table 8), the final picture of therapeutic success in our series is shown. In tables 1 and 3 we present the clinical results and the response of the spinal fluid in all the cases in which tryparsamide without fever therapy was the common factor of treatment. Thus, in 42 per cent of the cases the disease was considered to be clinically arrested, and in 53.8 per cent the spinal fluid became normal or was greatly improved. With the addition of fever therapy the figures are changed to show that in 54.3 per cent the disease was clinically arrested and the patient was able to return to the former level of efficiency with little or no defect and that in 71.6 per cent of the total group the spinal fluid was greatly improved or normal.

It is of some interest to compare the results in this series of patients who were treated with tryparsamide with those in our series who received malarial treatment.[15] The results obtained in both series are

TABLE 9.—*Comparison of Results of Treatment with Tryparsamide and Results of Malarial Therapy*

Series	Total No. of Patients Treated	Clinical Results, per Cent			Condition of Spinal Fluid, per Cent			
		Arrested	Stationary	Unimproved	Normal	Greatly Improved	Moderately Improved	Unimproved
Tryparsamide	81	42	29.6	28.4	37.5	16.3	10.0	36.2
Malaria.....	173	48.5	15.0	36.5	36.7	20.7	18.3	24.3

presented in table 9. The percentages in the two groups compare favorably with each other, but it must be pointed out that a few of the patients to whom tryparsamide was administered were included in the group who received malarial therapy. We wish to emphasize at this time that fever therapy following treatment with tryparsamide gives better results than any of the other combinations of methods. This may be due to the selection of patients who in most instances lived long enough to receive considerable amounts of treatment before fever therapy was instituted. In any case, it is true that most of them showed entirely normal spinal fluid, which, as already mentioned, is the best index of an arrest of the activity of the disease.

Mention should be made of the cases in which there was failure to respond favorably to therapy and in which, on the whole, the results were poor. These are extremely important and represent the best reason for the use of drastic methods in the treatment of dementia paralytica. It is this type of case which allows much speculation as to the best mode of therapy for this disorder. Experimental methods in neurosyphilis since the discovery of arsphenamine have been largely empirical, and one must keep in mind that the use of tryparsamide as

well as of malaria in the treatment of neurosyphilis is still on an experiential basis. We have already alluded to the fact that the mechanism of action of these methods of treatment is not clearly known.[18] It is not surprising, therefore, to find in our series a number of failures. It has been emphasized many times that a favorable social result is not to be expected in cases in which considerable damage to the parenchymatous tissue has already occurred, and poor clinical results are inevitable, even though the disease process has been arrested, as evidenced by negative reactions of the spinal fluid. At the same time it is apparent from an analysis of our series and from the experience of many authors that thoroughly good remissions of a rather permanent nature occur in a large percentage of cases. It is difficult to explain the favorable results obtained in some cases and the poor outcome in others. Furthermore, since there are no good prognostic criteria to apply before treatment is begun, the problem of the treatment in an individual case is empirical and the method of treatment is largely by trial and error. Nevertheless, it is our opinion that a considerable quantity of treatment and the lapse of time are two important factors in bringing about a normal spinal fluid.

We recognize that the situation is not always so simple and that there must be other considerations which come into play and exert influences on the final outcome in a case. For example, from our series we may cite the case of a patient who began treatment six months after the onset of symptoms of dementia paralytica and received 269 injections of tryparsamide during seven years without improvement. After having seventeen paroxysms of malaria fever in 1933 he was still unimproved clinically, and there was no change in the spinal fluid. He was finally committed to a state hospital. Another illustration is that of a patient who beginning nine months after the onset of symptoms of dementia paralytica was given 190 injections of tryparsamide during five years and then received a course of rat-bite fever therapy. Although the spinal fluid gave negative reactions promptly after the fever this patient continued to have seizures and died four years later. Still another example of a poor functional result is the case of a patient who began treatment within two months after the onset of the disease fifteen years ago; although he was still living in 1933 he was in a state of marked mental enfeeblement and was hardly able to find his way to the clinic. In this case, however, normality of the spinal fluid was secured and maintained after thirteen years of treatment, which consisted of 118 injections of arsphenamine and 8 intraspinal injections, followed by more than 100 injections of tryparsamide.

18. Solomon, H. C.; Epstein, S. H., and Berk, A.: The Differential Effects of Arsphenamine and Tryparsamide, Am. J. Syph. **17**:45 (Jan.) 1933.

We wish to emphasize that these are exceptional cases in our experience. However, they furnish a distinct challenge to the therapeutics of neurosyphilis as it stands today. Unfortunately, the ideal method of treatment has not yet been found, but we have had sufficient experience to be convinced that the best therapeutic results are obtained by the combination of tryparsamide and fever and that the long continued use of tryparsamide produces in the great majority of cases normality of the spinal fluid and an apparent arrest of the pathologic process. We say "apparent" arrest of the pathologic process advisedly, as there are no histologic studies reported in the literature concerning the effect of tryparsamide on the pathologic changes in the brain, and the conclusions must therefore be based on assumptions drawn from serologic and clinical observations.

SUMMARY

An analysis is presented of the effect of tryparsamide therapy in a series of 81 cases of dementia paralytica in which treatment was begun between the years 1923 and 1930 and in which the condition was determined in 1933. Some of the patients received other forms of antisyphilitic treatment (exclusive of fever therapy) prior to or during treatment with tryparsamide.

In 34 of the patients (42 per cent) the condition was considered from the clinical standpoint to be arrested; in 24 (29.6 per cent), to be stationary, and in 23 (28.4 per cent), to be unimproved.

In the course of the years, 14 patients died, but in only 5 cases did death appear to be due to unarrested dementia paralytica.

The spinal fluid became normal in 30 patients (37.5 per cent) and was greatly improved in 13 (16.3 per cent), moderately improved in 8 (10 per cent) and unimproved in 29 (36.2 per cent).

There were 64 patients in the series who received no other treatment than by tryparsamide. In 18 (26.7 per cent) of these the spinal fluid became normal; in 10 (15.9 per cent) it was greatly improved; in 7 (11.1 per cent) it was moderately improved, and in 28 (44.4 per cent) it showed no change. In 1 case a specimen of the fluid could not be obtained.

The period elapsing between the beginning of treatment and the time when the spinal fluid became normal varied from less than a year to more than nine years. The number of injections of tryparsamide given up to the time when the fluid became normal varied from 20 to 230. No significant difference in results was found in patients receiving tryparsamide alone and in those receiving other types of antisyphilitic treatment, other than fever therapy, in conjunction with tryparsamide.

Seventeen patients of the series who did not respond satisfactorily to tryparsamide were subsequently given fever therapy with strikingly

beneficial results. The spinal fluid became normal in 12 patients, was greatly improved in 3 and was moderately improved in 2, whereas before fever therapy the spinal fluid was unimproved in 15 and only moderately improved in 2. The clinical improvement was equally striking. Before fever therapy 14 patients were considered to show no improvement. After fever therapy 8 showed the disease to be arrested, and in 6 it was stationary. Before fever treatment in 3 patients the disease was considered to be stationary. In 2 of these it was later considered to be arrested without showing notable defect, and in 1 the condition remained unchanged.

The results of tryparsamide treatment in this series were compared with the results in a series of 173 patients with dementia paralytica treated by us and reported on in another paper.[15] The clinical outcome and the response of the spinal fluid did not differ to an extent that can be considered significant.

CONCLUSIONS

From the observations reported we conclude:

1. Tryparsamide has a definitely beneficial effect both clinically and serologically in cases of dementia paralytica.

2. The clinical results of treatment with tryparsamide do not differ greatly from those obtained by malarial therapy.

3. The patients treated with tryparsamide and subsequently given malarial treatment show a percentage of improvement that is unusually high.

4. Combined treatment with tryparsamide and malaria in many cases is far superior to the use of tryparsamide alone, and the subsequent use of malaria may give a satisfying therapeutic result in patients who do not respond favorably to tryparsamide alone.

DISCUSSION

Dr. H. H. Merritt: This presentation shows that another strong agent against the spirochete is available in tryparsamide. Was there any selection of the patients who received tryparsamide as against those who were given malarial therapy? Were any of the patients treated with tryparsamide hospitalized, or were they all ambulatory? If there was no selection it would seem that tryparsamide is the treatment of choice, since it does not necessitate hospitalization.

Dr. D. Gregg: Is it possible clinically to separate the patients who have or have not extensive parenchymatous damage, or is it assumed that those who are not benefited by treatment are those with such damage?

Dr. H. R. Viets: In this series tryparsamide was usually used before fever therapy. Have the authors had any experience with the use of fever first followed by tryparsamide? Are the results more rapid with malaria than with tryparsamide?

DR. S. H. EPSTEIN: In answer to Dr. Merritt's question regarding the selection of cases, the majority of the patients treated with tryparsamide were ambulatory. Most of those who received malarial therapy were hospitalized, but even in this group automatic selection of cases occurred because of the limitations of hospital facilities. Therefore, for practical purposes it is fair to say that there was no significant difference between the patients in the group given malarial therapy and those in the group receiving tryparsamide.

In reply to Dr. Gregg's question, all that can be said is that it is not possible to predict from the clinical standpoint which patient is not likely to do well. It is assumed that a poor clinical result is due to the extent of parenchymatous damage already existing before treatment.

Dr. Viets raised the question of the sequence of treatment. I neglected to mention that the series given malarial treatment includes patients who were subsequently treated with tryparsamide. The results shown by these patients were similar to those in the group given tryparsamide alone. About the same amount of time was required in the two series of cases to achieve a good clinical and serologic result. It is to be emphasized, however, that those patients who did not do well after receiving tryparsamide showed a striking improvement when malaria was given subsequently. Just why this occurs is by no means clear.

DR. O. RAEDER: The onset of symptoms dated back fifteen years in one case. In which group does that patient come?

DR. S. H. EPSTEIN: That patient was treated by intraspinal, intraventricular and intracisternal injections and did not do well until tryparsamide was introduced. From that time on he showed improvement which persisted.

INTRACRANIAL ARTERIOVENOUS FISTULA

III. DIAGNOSIS BY DISCOVERY OF ARTERIAL BLOOD IN JUGULAR VEINS

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A review of the clinical and postmortem features in a case of intracranial arteriovenous fistula observed by Moersch and Kernohan in 1930 suggested to us the possibility that the diagnosis in similar conditions could be made clinically by study of the oxygen content of the blood in the jugular veins. The need for accurate diagnostic methods is evidenced by the fact that in most cases which have been reported in the literature the diagnosis was made either at the time of surgical exploration or at necropsy. We use the term "arteriovenous fistula" to designate any abnormal communication between an artery and a vein by means of which arterial blood enters the vein without passing through a capillary bed. Intracranial arteriovenous fistulas are essentially the same as arteriovenous fistulas situated in other parts of the body. The arrangement of the vessels varies markedly, but the fundamental condition and the resulting processes in the vascular system are similar, whether the fistula is in the foot or in the cranial cavity.

One of us (Horton) previously had been able to diagnose the presence of arteriovenous fistula in an extremity by study of the oxygen content of blood from the superficial and deep veins of the involved extremity. Regarding the head as a fifth extremity, we thought it reasonable to believe that if abnormal communications existed between arteries and veins within the cranial cavity, so that blood passed from the arterial to the venous system without interposition of a capillary bed, blood from the internal jugular vein would show an admixture of arterial and venous blood which could be demonstrated by means of oxygen

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determination of the blood (gasometric method of Van Slyke). By means of this determination we have been able to diagnose intracranial arteriovenous fistula. The diagnosis has been verified at surgical exploration in cases in which such a lesion was not suspected on routine neurologic examination, and in which an audible intracranial bruit and increased extracranial vascularity were absent. Intracranial arteriovenous fistulas represent the most serious type of intracranial vascular anomaly, and the determination mentioned enables the neurologist and the neurosurgeon to distinguish this lesion clinically from other intracranial anomalies.

Intracranial arteriovenous fistulas have been reported under various names, such as "angioma cavernosum," "arteriovenous aneurysmal varices," "angioma arteriale," "angioma arteriale racemosum," "arteriovenous aneurysm" and "arteriovenous angioma," but these names all represent the same type of lesion, namely, a condition in which blood from an artery enters a connecting vein without interposition of a capillary bed. The neurosurgeon frequently has commented on the fact that in cases of intracranial arteriovenous fistula one can see through the thin-walled veins and can detect the pulsing red arterial blood against a background of dark venous blood, and Cushing, while exploring the great vessels of the neck in a well advanced case of intracranial arteriovenous fistula (case 9 in his series; cases which he prefers to call "angioma arteriale"), observed that the internal jugular vein was markedly enlarged, that it appeared lighter in color than was normal, and that what appeared to be a current of arterial blood was passing down in the venous stream. One of us (Adson), while exploring the great vessels of the neck in a similar case, observed the same phenomenon. In addition, the internal jugular vein was pulsating almost as vigorously as the common carotid artery. The oxygen saturation of blood removed from the internal jugular vein was 95 per cent.[1] This patient gave no evidence of increased extracranial vascularity, but a loud, continuous bruit could be heard over both sides of the neck, somewhat louder on the right side. The right external jugular vein also pulsated. The oxygen saturation of its blood was 79.9 per cent. Examination of the ocular fundi showed the veins in the right fundus to be of a brighter red than those in the left fundus. This was due to the fact that the veins of the right fundus contained arterial blood. Edema of the disks was not present. Neurologic examination in this particular case gave

1. The oxygen saturation of the blood in the internal jugular veins of normal subjects is 62 per cent. The oxygen saturation of normal arterial blood is approximately 95 per cent.

objectively negative results, but there can be no doubt that the patient had an intracranial arteriovenous fistula.

Complicated studies of the oxygen content by the Van Slyke method are frequently not necessary, for in many cases the color of blood drawn from a vein that is involved in an arteriovenous fistula is of a sufficiently brighter red than normal venous blood to allow the diagnosis to be made on this basis alone.

QUININE THERAPY IN CASES OF MULTIPLE SCLEROSIS OVER A FIVE YEAR PERIOD

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The study of quinine therapy in cases of multiple sclerosis has been in progress for five years. In an earlier report,[1] presented about fourteen months after the study was commenced, it was stated that quinine therapy appeared to have promise. The experience of five years with forty-nine patients seems to justify the conclusion that quinine is beneficial in cases of multiple sclerosis, particularly in the early stages.

The hypothetic and theoretical grounds for the employment of quinine were outlined in the communication referred to. They may be briefly recapitulated as follows: Marburg's idea that the lesions in cases of multiple sclerosis might be produced by the action of a circulating lipolytic agent was adopted as a working hypothesis, and experiments were undertaken to test its value. These experiments have given evidence supporting the idea, although they are still not completed. It had already been discovered that some lipases of the blood could be inactivated by quinine, and on these grounds, hypothetic as they were, treatment with quinine was undertaken.

RÔLE OF SPONTANEOUS REMISSIONS

The incidence of spontaneous remissions forms, of course, a serious obstacle in the evaluation of any type of treatment; this fact must play a large part in the difficulty which has always existed in coming to conclusions and in the prevalent lack of faith in any kind of therapy for multiple sclerosis. Yet the search for successful treatment should neither be abandoned nor be taken lightly for this reason, nor should scientific skepticism be replaced by sheer pessimism, as has recently been stressed by Weinberg.[2] It might even be profitable to take the view that any therapeutic method the use of which is frequently linked with remissions or improvements is worthy of study in so tragic a disease

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From the Neurological Institute and the Department of Neurology, College of Physicians and Surgeons, Columbia University.

1. Brickner, Richard M.: Experiences in the Treatment of Multiple Sclerosis with Quinine Hydrochloride, Arch. Neurol. & Psychiat. **28**:125 (July) 1932.

2. Weinberg, Max H.: Lecithin Treatment of Some Multiple Sclerosis Syndromes, J. Nerv. & Ment. Dis. **79**:264 (March) 1934.

as this, even though one cannot learn at the time whether the remissions are spontaneous or not.

In the present investigation the remission phase of the problem was approached in part by considering not only the clinical improvement made by patients but also the degree to which new symptoms occurred and old ones grew worse while treatment was in progress. In the forty-nine patients reported on—treated for from six months to five years—the incidence of these manifestations was of minor degree; a result of this nature appears to be independent of spontaneous remissions.

For similar reasons, observation was made of the speed and completeness with which patients recovered from the exacerbations associated with colds and other illnesses, and consideration was given to the effects of severe physical shock and of unusual physical exertion, such as the driving of a car across the continent. By these criteria also the results appeared to be favorable. Concerning actual clinical improvement, it was thought that if it usually began within a more or less regular interval after the institution of treatment and that if the newer symptoms improved more rapidly and more completely than the old ones the indications would be that the treatment was responsible rather than the spontaneous remissions. It appears that these qualifications have been met. The aggregated evidence supports the view that it is the treatment which is effective.

It seems difficult to select criteria that will answer the question of remission any better in so capricious a disease as multiple sclerosis. Its chronicity, the much longer duration of some symptoms than of others, the fact that some symptoms represent the late stage scar while others indicate fresh activity of the disease, the progressive damage that may be caused by dense gliosis and the eventual necrosis of the nerve cells all make it unreasonable to expect such decisive indications of improvement as are shown, for example, by the blood count in cases of pernicious anemia in which liver therapy has been used.

One important phase of the study which has not as yet been made is the systematic analysis of an adequately large control series. This is an omission not of design but of necessity. Because of the relative paucity of clearcut cases of the disease it has been found impossible to accumulate more than one fairly large group. For control purposes it has been found necessary to resort to general experience, to reports in the literature and to the histories of the patients under my observation who were sensitive to quinine and could not be treated with it. These sources are all discouraging and support the idea that quinine therapy has been helpful. But such control material is not amenable to the systematic type of study which is essential for correct evaluation.

RESULTS

SYMPTOMATIC ANALYSIS

The study has been conducted from the beginning by considering the patients in two different ways: as sick persons and as carriers of groups of symptoms. Only the latter method permits separate evaluation of the courses of old and new symptoms, with adequately controlled theoretical analysis of the effects of treatment; the former method, however, is better adapted to assaying the degree of practical usefulness of the therapy. An effort has also been made to classify the patients and the results according to Marburg's scheme. He divided his cases into four groups: (1) the stationary type; (2) the chronic and progressive type, without remissions; (3) the typical remission type, which develops by repeated outbursts of the disease, with intervening remissions, and (4) the acute, rapidly progressing type. It has not been easy to make an accurate classification of this sort, because the groups merge with one another, especially when they are studied symptom by symptom, as has been done in the present investigation. Few are entirely stationary and few run their course without remission of at least some of the symptoms. Only two of the cases in the present series belong exclusively in Marburg's group 3, the histories showing several outbursts of the disease with periods of comparative freedom from symptoms in between. (They are indicated by 5 instead of 3 in table 1.) In most of the cases there were symptoms of one kind or another continuously, with remissions and fluctuations of varying grades of completeness (indicated by 3 in table 1). There are a few other cases that may belong to Marburg's third group (my group 5), but which cannot be placed there with assurance. In most instances it was found impossible to assign a case definitely to any one group; often a case appears to belong in a certain group at an early stage of the disease and to another later on. Altogether this classification, which is the only one that has been used to any extent in studying multiple sclerosis in the past, has been found in the present study to be less useful than the other schemes already outlined.

The forty-nine patients studied had a total of three hundred and eight symptoms. All but one of the patients have been under treatment for at least six months and many for much longer. A special blank (fig. 1) has been used to obtain easily read chronological histories.

No other means of treatment has been used concomitantly with the administration of quinine. Even rest in bed has been kept at a minimum.

The symptomatic results are given in table 1, which is included at full length to serve as a partial summary of the individual cases and also to illustrate the method of study.

The clinical diagnosis of multiple sclerosis was agreed on by several observers in all the cases included in this series. I have followed all

TABLE 1.—*Analysis of Symptomatic Results* *

Case	Duration of Treatment	Duration of Symptom Before Treatment	Symptom	Improved	Worse	Unchanged	Unknown	New Symptoms Appearing During Treatment Symptom	Duration	Working	Ability to Work Prior to Treatment	Clinical Group	Age, Years
B. A.	1 yr., 9 mos.	3 yrs., 8 mos.	Frequency	+	..	..	..	.....	....	0	0	2, 3, 5	23
		2 yrs., 8 mos.	Spastic gait*	..	+								
		8 mos.	Imbalance*	..	+								
		Long	Intention tremor, right and left*	..	+								
B. S. (t)	4 yrs., 6 mos.	2 yrs.	Imbalance	..	..	+	..	.....	....	+	+	2, 3, 5	30
		14 mos.	Hypesthesia of right hand	4 +						Heavy office work			
		Long	Fatigue	..	..	+							
L. G. (t)	3 yrs., 6 mos.	1 yr.	Imbalance*	4 +			..	.....	....	+	0 for 1 yr.	3, 5	15
		1 yr.	Hypesthesia of whole left side*	4 +						Salesman			
		1 yr.	Aphasia, mild	4 +									
		9 mos.	Uncontrollable laughter	..	..	+							
		9 mos.	Frequency	4 +									
		9 mos.	Hesitancy	4 +									
		6 mos.	Weakness, right leg*	4 +									
		6 mos.	Impotence	..	..	+							
		6 mos.	Ataxia of right hand	4 +									
L. S. (t)	3 yrs., 6 mos.	4 yrs., 3 mos.	Spastic gait*	..	+	..	..	.....	....	0	0	2, 3	29
		4 yrs., 3 mos.	Intention tremor, right and left	..	+								
		4 yrs.	Slight scanning	..	..	+							
		1 mo.	Paralysis of left facial and left abducens nerve	4 +									
		Long	Hesitancy*	..	..	+							
		Long	Frequency*	..	..	+							
C. B.	2 yrs.	8 yrs.	Vertigo	..	..	+	..	.....	....	+	+	1, 2, 3	37
		5 yrs.	Hesitancy, occasional	..	..	+				Housework			
		2 yrs., 3 mos.	Insecurity on feet	..	..	+							
		2 yrs., 3 mos.	Dysarthria*	..	..	+							
		2 yrs., 2 mos.	Weakness; ataxia of hands	..	..	+							
		8 mos.	Marked imbalance	+									
		8 mos.	Diplopia	..	..	+							
		5 mos.	Dysphagia	+									
		1 mo.	Tingling of whole left side	+									
G. M.	1 mo.	13 yrs.	Spastic paraplegia	..	..	+	..	.....	....	0	0	2	32
		Recent	Scanning	4 +									
		Long	Intention tremor	..	..	+							
C. P.	1 yr.	1 yr., 1 mo.	Spastic gait	4 +	..	..	..	.....	....	+	+	2, 5	52
											0	1, 2, 5	38

	1 yr.	1 yr., 1 mo.	Spastic gait	4 +	..	..	..	.....	....	+	+	2, 5	52

M. G.	1½ yrs.	2 yrs., 4 mos.	Frequency	+	..	..	..	.....	....	0	0	1, 2, 5	38
		1 yr., 8 mos.	Fatigue	..	..	+							
		1 yr.	Spastic gait*	+									
		1 yr.	Imbalance*	+									
		6 mos.	Weakness of right arm	..	..	+							
		6 mos.	Hypesthesia of right arm	..	..	+							
J. P. F.	.....	1 mo.	Diplopia	4 +	..	..	..	.....	....	..	..	.....	..
										+	+	1, 2, 3	26
W. W. (t)	4 yrs.	10 yrs.	Spastic gait	..	..	+	..	.....	....	Legal adviser			
		10 yrs.	Imbalance	..	..	+							
		6 yrs.	Intention tremor	..	..	+							
		5 yrs.	Hypesthesia of legs	+									
		4-5 yrs.	Impotence	..	..	+							
		2 yrs.	Frequency	+									
		2 yrs.	Hesitancy	+									
		Long	Hypesthesia of hands	+									
		Long	Fatigue	..	+								
L. O	10 mos.	10 mos.	Flexion contracture of legs	+	..	..	..	....	....	0	0	2, 3	29
		10 mos.	Paralysis of legs	+									
		10 mos.	Incontinence of urine and feces	..	+								
		Long	Euphoria	..	..	+							
F. G.	.....	2 yrs., 6 mos.	Visual dimness	+	..	..	..	.....	....	..	..	.....	..
		2 yrs., 6 mos.	Hypesthesia of all extremities	..	..	+							
		2 yrs., 6 mos.	Imbalance	..	..	+							
H. W.	1 yr.	4 yrs.	Spastic paraplegia	..	..	+	..	.....	....	Deceased	..	2	22
		4 yrs.	Intention tremor, right	..	..	+							
		1 mo.	Intention tremor, left	..	+								
		Long	Head tremor	..	..	+							
W. S. (t)	4 yrs., 3 mos.	5 yrs.	Spastic gait*	..	+	..	..	Tingling of left leg; hypesthesia of both legs; general weakness	2 wks.; ? still present	0	0	2, 3, 5	14
		5 yrs.	Imbalance*	..	+								
		5 yrs.	Diplopia*	..	..	+							
		5 yrs.	Intention tremor*	..	+								
		Long	Urgency	..	..	+							
S. S. S.	9 mos.	2 yrs., 10 mos.	Diplopia	..	..	..	+	Hypesthesia of hands	?	..	..	3, 5 (?)	22
		2 yrs., 10 mos.	Fatigue	..	..	..	+						
		2 yrs.	Imbalance*	4 +									
		2 yrs.	Spastic gait*	4 +									
C. O.	1 yr.	4 yrs.	Imbalance	..	..	+	..	.....	....	Died of pneumonia	..	2	27
		4 yrs.	Astasia	..	..	+							
		4 yrs.	Head tremor	..	..	+							
		4 yrs.	Intention tremor	..	..	+							
		Recent	Scanning	+									

* In table 1, "spastic gait" denotes a gait impaired by spasticity, without complete incapacity. "Spastic paraplegia" denotes incapacity to walk, even with assistance. Frequency and urgency of urination are considered as one symptom, since it was found that they usually appeared and disappeared together. Hesitancy and slight vesical incontinence are also paired as one symptom for the same reason. The former pair may be due to malfunction of the musculature of the bladder itself, and the latter, to that of the vesical sphincter. Marked improvement or entire disappearance of a symptom is indicated by 4 + and slight or moderate improvement by a + sign. Symptoms marked with an asterisk are recurrent. Patients who have remained on treatment up to date are indicated by (t) next to the patient's initials. (Not all of the patients are still under treatment; some have terminated treatment for reasons given. Throughout, comments refer to patients at the latest date of treatment, whether it is the present moment or an earlier date of termination.) Marburg's groups are indicated as follows: stationary, 1; chronic progressive, 2; acute with rapid course, 4; outburst-remission, 5. The type which slowly progresses with fluctuations and remissions of single symptoms, which is so common in the present series and which Marburg does not seem to include, is indicated by the number 3. The ages given in the last column refer to the onset of the disease.

TABLE 1.—*Analysis of Symptomatic Results—Continued*

Case	Duration of Treatment	Duration of Symptom Before Treatment	Symptom	Improved	Worse	Unchanged	Unknown	New Symptoms Appearing During Treatment Symptom	Duration	Working	Ability to Work Prior to Treatment	Clinical Group	Age, Years
R. P. (t)	3½ yrs.	1 yr., 4 mos.	Fatigue of legs	+	..	..	..	.....	....	+	For 1 yr. could work only a little	1, 2, 3	25
		1 yr., 3 mos.	Dragging of left foot	4 +						Taxi-driver			
		1 yr., 3 mos.	Imbalance	4 +									
		3 mos.	Poor memory	..	..	..	+						
		1 wk.	Diplopia	4 +									
		Recent	Hesitancy	4 +									
		Recent	Weakness of left hand	4 +									
		Recent	Intention tremor, slight	4 +									
N. G.	2 mos.	2 mos.	Intention tremor, left*	..	..	+	..	.....	....	..	..	5	19
		2 mos.	Imbalance*	+									
		2 mos.	Spastic gait*	+									
		2 mos.	Scanning	+									
W. K. (t)	3½ yrs.	1 yr., 3 mos.	Spastic gait	4 +	..	..	..	.....	....	+ Outdoor salesman	0 for 11 mos.	2, 3	29
		1 yr., 3 mos.	Imbalance	4 +									
		1 yr., 3 mos.	Weakness of legs	4 +									
		9 mos.	Diplopia	+									
		6 mos.	Hesitancy	4 +									
		3 wks.	Intention tremor, right and left	4 +									
		1 wk.	Unable to walk alone	4 +									
		Recent	Girdle sensation in abdomen	..	..	..	+						
F. D.	1 yr., 3 mos.	3 yrs.	Imbalance	..	+	..	..	Hypesthesia of left side of face	2 mos.	Deceased	..	2, 3, 5	27
		3 yrs.	Spastic gait	..	+								
		1 yr.	Fatigue	..	+								
		1 yr.	Extreme obstipation	..	..	+							
		6 mos.	Hypesthesia of all fingers	..	..	+							
		Long	Intention tremor	..	..	+							
		Recent	Incontinence of urine	+									
		Recent	Scanning	+									
A. N.	9 mos.	3 yrs.	Scanning	+	..	..	..	.....	....	Could work	0	2, 3, 5 (?)	26
		2 yrs., 9 mos.	Frequency	4 +									
		1 yr.	Imbalance	4 +									
		1 yr.	Spastic gait	4 +									
		1 yr.	Intention tremor, right and left	..	+								
		7 mos.	Aphasia, mild	4 +									
		Recent	Diplopia	+									

R. C.	3½ yrs.	4 yrs., 6 mos.	Fatigue	..	..	+	..	.....	....	0	0	2, 5 (?)	21
		2 yrs., 6 mos.	Spastic paraplegia	+									
		1 yr., 6 mos.	Intention tremor, right and left	+									
		1 yr., 6 mos.	Blurred vision	+									
		1 yr., 4 mos.	Scanning	+									
		1 yr., 4 mos.	Dysphagia	..	+								
		1 yr.	Hesitancy	..	+								
		4 mos.	Palsy of left abducens nerve	..	+								
		Long	Euphoria	..	..	+							
K. L. S.	6 mos.	3 yrs., 6 mos.	Imbalance	..	..	+	..	.....	....	0	0	3	26
		3 yrs., 6 mos.	Weakness of legs	..	..	+							
		1 yr., 10 mos.	Intention tremor, right and left	..	..	+							
		1 mo.	Head tremor	+									
		Long	Spastic paraplegia	..	+								
		Long	Fatigue	..	..	+							
		Recent	Athetosis of right hand	+									
W. M.	8 mos.	11 yrs.	Numbness of fingers	..	..	..	+	.....	....	Could work	0	1, 2, 3	27
		10 yrs.	Weakness of left leg*	..	..	..	+						
		10 yrs.	Fatigue	+									
		6 yrs.	Impotence	..	..	+							
		3 yrs.	Frequency	+									
L. E.	8 mos.	2 yrs., 6 mos.	Frequency	+	..	..	..	.....	....	0	0	2	38
		2 yrs.	Spastic paraplegia	..	..	+							
		2 yrs.	Imbalance	..	..	+							
		1 yr.	Intention tremor, right and left	+									
R. H.	1½ yrs.	4 yrs.	Impotence	..	..	+	..	.....	....	+	?	1, 2, 5	34
		4 yrs.	Weakness of knees	..	..	+				Outdoor work			
		1 yr.	Weakness of whole right leg*	4 +									
		1 yr.	Imbalance	+									
		6 mos.	Diplopia	..	..	+							
		6 mos.	Intention tremor, right and left*	+									
		6 mos.	Hypesthesia of hands and feet	+									
P. B. (t)	3 yrs.	2 yrs.	Frequency	4 +	..	..	..	.....	....	+	0	3	40
		2 yrs.	Imbalance	4 +						Painter			
		2 yrs.	Weakness of right leg	4 +									
		1 yr., 6 mos.	Fatigue	4 +									
		1 yr., 6 mos.	Incontinence, slight	4 +									
F. P. (t)	3½ yrs.	2 yrs., 6 mos.	Spastic gait	4 +	..	..	..	Dysphagia	In 1-14 day spells	+	0	3, 5 (?)	31
		2 yrs., 6 mos.	Imbalance	4 +						Nursing sick family; heavy housework			
		6 mos.	Hypesthesia of left leg	4 +									
		1 mo.	Hypesthesia of hands	4 +									
		Long	Girdle sensation	4 +									

TABLE 1.—*Analysis of Symptomatic Results—Continued*

Case	Duration of Treatment	Duration of Symptom Before Treatment	Symptom	Improved	Worse	Unchanged	Unknown	New Symptoms Appearing During Treatment Symptom	Duration	Working	Ability to Work Prior to Treatment	Clinical Group	Age, Years
W. B. (t)	3¼ yrs.	4 yrs., 6 mos.	Heaviness of legs*	+	..	..	..	Visual dimness of right eye; hypesthesia of left side of chest	Still present	+ Light jobs; dressing dolls for Christmas	?	2, 3, 5	29
		3 yrs., 9 mos.	Frequency	+									
		3 yrs., 6 mos.	Imbalance*	+									
		3 yrs., 1 mo.	Blurred vision	+									
		3 yrs.	Fatigue	+									
		2 yrs.	Spells of depression	+					Still present				
		8 mos.	Hypesthesia of four extremities*	4 +									
		1 mo.	Intention tremor, right*	4 +									
I. H.	6 mos.	10 mos.	Frequency	..	..	+	..	.....	....	0	0	2, 3	Late teens
		10 mos.	Incontinence of urine, slight	..	..	+							
		6 mos.	Spastic paraplegia	..	..	+							
		6 mos.	Diplopia	4 +									
		Recent	Intention tremor, right and left	..	..	+							
		Recent	Impotence	4 +									
J. A. (t)	2½ yrs.	1 yr., 7 mos.	Weakness of lower extremities	..	+	..	..	.....	....	0	0	3, 5	27
		1 yr., 7 mos.	Imbalance	..	+								
		1 yr., 7 mos.	Frequency	+									
		1 yr., 7 mos.	Hesitancy	+	..								
		1 yr., 6 mos.	Rectal anesthesia	4 +									
		9 mos.	Intention tremor, right	..	+								
		9 mos.	Weakness of right hand	+									
		4 mos.	Dysarthria	4 +									
J. C.	6 mos.	Recent	Imbalance	..	+	..	..	.....	....	0	0	4	18
		Recent	Spastic paraplegia	..	+								
		Recent	Intention tremor, right and left*	..	+								
		Recent	Diplopia	..	..	..	+						
		Recent	Frequency	..	..	..	+						
		Recent	Scanning	..	..	+							
H. E. (t)	1½ yrs.	1 yr., 2 mos.	Spasticity of lower extremities*	+	..	..	..	.....	....	0	0	2, 5	34
		1 yr., 2 mos.	Imbalance	+									
		1 yr., 2 mos.	Weakness of lower extremities	+									
		1 yr., 2 mos.	Hypesthesia of lower extremities*	..	..	+							
		1 yr., 2 mos.	Hypesthesia of hands	4 +									
		1 yr., 2 mos.	Intention tremor, right and left	4 +									
		1 yr., 2 mos.	Frequency	..	..	+							
		1 yr., 2 mos.	Hesitancy	4 +									
		1 yr., 2 mos.	Fatigue	+									

P. E. (t)	6 mos.	1 yr., 9 mos.	Imbalance	4 +	..	..	..	.....	....	0	0	1, 3	28
		1 yr., 9 mos.	Spastic gait	4 +									
		1 yr., 9 mos.	Scanning	+									
		1 yr., 9 mos.	Intention tremor, right and left	4 +									
		1 yr., 9 mos.	Hesitancy	4 +									
		1 yr., 9 mos.	Impotence	..	..	+							
		7 mos.	Head tremor	4 +									
		7 mos.	Diplopia	+									
		4 mos.	Visual bobbing	+									
		3 mos.	Hypesthesia of hands and feet	4 +									
F. F.	9 mos.	8 yrs.	Dim vision	..	..	+	..	.....	....	0	0	3, 5	28
		2 mos.	Imbalance*	4 +									
		2 mos.	Weakness of lower extremities*	4 +									
		2 mos.	Hypesthesia from hips down	+									
		2 mos.	Occasional body tremor	..	..	+							
		2 mos.	Frequency	4 +									
		2 mos.	Incontinence of urine occasional and slight	4 +									
		Recent	Weakness of back	+									
		Recent	Scanning	..	..	..	+						
D. L. (t)	9 mos.	5 yrs., 7 mos.	Imbalance	..	..	+	..	.....	....	0	0	1, 2, 3	28
		5 yrs., 7 mos.	Weakness of left lower extremity	..	..	+							
		4 yrs.	Frequency	4 +									
		3 yrs.	Fatigue	..	+								
		Long	Spasticity of lower extremities	..	..	+							
M. K. (t)	1 yr., 10 mos.	4 yrs., 1 mo.	Hypesthesia of abdomen	+	..	..	..	Dysphagia, slight	Still present	Could work	Could have worked	1, 3, 5	31
		4 yrs., 1 mo.	Hypesthesia of right hand	+									
		4 yrs., 1 mo.	Fatigue	+									
		4 yrs., 1 mo.	Imbalance	+									
		3 yrs., 11 mos.	Weakness of lower extremities	+									
		2 yrs.	Dysarthria	..	..	+							
		3 mos.	Nocturnal visual dimness	+									
S. B. (t)	2 yrs.	2 yrs.	Fatigue	4 +	..	..	..	.....	....	+ Outdoor salesman	+	3	27
		1 yr., 7 mos.	Frequency	4 +									
		1 mo.	Imbalance, slight	4 +									
		Recent	Scanning, slight	+									
		Recent	Diplopia, occasional	4 +									
		Recent	Hypesthesia above knees	4 +									
		Recent	Emotional instability	..	..	+							

TABLE 1.—*Analysis of Symptomatic Results—Continued*

Case	Duration of Treatment	Duration of Symptom Before Treatment	Symptom	Improved	Worse	Unchanged	Unknown	New Symptoms Appearing During Treatment Symptom	Duration	Working	Ability to Work Prior to Treatment	Clinical Group	Age, Years
M. N.	1 yr., 9 mos.	3 yrs.	Coldness of lower extremities	..	..	+	..	.....	....	Died of infected decubitus ulcer	..	2, 4	36
		2 yrs., 6 mos.	Spastic gait	..	+								
		2 yrs., 6 mos.	Weakness of lower extremities	..	+								
		2 yrs., 6 mos.	Imbalance	..	+								
		2 yrs., 3 mos.	Intention tremor, right and left	..	+								
		2 yrs., 3 mos.	Hesitancy	..	+								
		2 yrs., 3 mos.	Frequency	..	+								
		2 yrs., 3 mos.	Incontinence of urine, slight	..	+								
		2 yrs., 3 mos.	Visual bobbing	..	..	+							
		2 yrs., 3 mos.	Anosmia	..	..	+							
		2 yrs.	Impotence	..	..	+							
S. P. (t)	1 yr.	7 mos.	Hypesthesia of right hand	+	..	..	..	.....	....	+ Radio operator	+	1, 2, 5	27
		3 mos.	Vertigo	..	..	..	+						
		3 mos.	Imbalance	..	..	+							
		2 mos.	Fatigue	+									
K. O. (t)	1 yr.	5 yrs., 6 mos.	Weakness of left leg	4 +	..	..	..	Dysesthesia of right thigh	Still present	Could work	0	2, 5	28
		5 yrs., 6 mos.	Imbalance	4 +									
		5 yrs., 6 mos.	Vertigo	+									
		5 yrs., 6 mos.	Hypesthesia of left fingers	4 +	Began prior to improve to treatment								
		4 yrs.	Fatigue	4 +									
		4 yrs.	Urgency	4 +									
		4 yrs.	Incontinence of urine, slight	4 +									
		4 yrs.	Intention tremor, right and left	4 +									
		1 yr.	Dysesthesia of right leg	4 +									
		1 yr.	Weakness of arms	4 +									
		2 mos.	Hypesthesia of all toes	4 +									
		1 mo.	Hypesthesia of abdomen and left thigh	4 +									
		Long	Hesitancy*	4 +									
M. S. (t)	2 yrs.	3 yrs., 8 mos.	Hypesthesia of right knee*	..	..	+	..	Head tremor	1 yr.	Could except for eyes	+	3, 5	20
		3 yrs.	Imbalance	+									
		2 yrs.	Hesitancy	..	..	+	..	Hypesthesia from left sixth rib down	6 wks.				
		1 yr., 6 mos.	Visual dimness, diurnal	..	..	+		Paralysis of right abducens nerve; diplopia	3 wks.				
		1 yr., 3 mos.	Electric symptoms	4 +					5 mos.				
		1 yr.	Intention tremor, right and left	4 +									
R. S. (t)	1 yr.	1 yr., 9 mos.	Intention tremor, right	4 +	..	..	..	.....	....	Could work	Could have worked	1, 2, 3, 5	17
		9 mos.	Weakness of lower extremities	4 +									
		3 mos.	Imbalance	4 +									
		3 mos.	Tinnitus	..		+							
		3 mos.	Fatigue	4 +	Began before to improve treatment								
		3 mos.	Hesitancy	4 +	Began before to improve treatment								

		3 mos.	Hesitancy	4 +				Began before treatment	to improve				
				4 +				Began before treatment	to improve				

V. Z. (t)	1 yr., 5 mos.	3 yrs.	Weakness of lower extremities	..	..	+	..	Electric symptoms	Still present	+ Light housework	Before (?)	1, 2, 3, 5	32
		3 yrs.	Imbalance	+									
		3 yrs.	Hypesthesia of all fingers	..	..								
		3 yrs.	Intention tremor, right and left	+									
		1 yr.	Blurred vision	4 +									
		3 mos.	Dysesthesia of feet	4 +									
		2 mos.	Frequency	+									
		2 mos.	Hesitancy	..	..	+							
		Long	Fatigue	..	.	+							
C. Z.	6 mos.	9 yrs.	Positive scotoma	..	..	..	+	.....	....	+ Farming	Probably could have	2	33
		6 yrs.	Fatigue	+									
		3 yrs., 8 mos.	Spastic right leg	..	..	+							
		3 yrs., 8 mos.	Weakness of right leg	+									
		3 yrs., 8 mos.	Frequency	..	..	+							
		2 yrs., 8 mos.	Hesitancy	+									
		Long	Hypesthesia of all fingers	..	..	..	+						
J. M. (t)	5 yrs.	1 yr., 6 mos.	Hypesthesia of all extremities	4 +	..	..	..	.....	....	+ Collector	0	3	23
		1 yr., 6 mos.	Hesitancy	4 +									
		Long	Intention tremor, right and left	4 +									
		Long	Euphoria	..	..	+							
		Recent	Spastic paraplegia	4 +									
		Recent	Incontinence of feces, slight	4 +									
		Recent	Dimness of vision, left	4 +									
		Recent	Dimness of vision, right	4 +									
		Recent	Impotence	..	..	+							
G. R. (t)	2 yrs.	8 yrs.	Stiffness of hands*	..	..	+	..	Dysesthesia of back	Still present	+ Sales-woman	Could have worked	2, 5	18
		8 yrs.	Hypesthesia of many parts*	..	..	..	+	Left foot drop, partial	Still present				
		8 yrs.	Fatigue*	..	..	+	..						
		8 yrs.	Foot drop, right*	..	..	+							
		7 mos.	Cataplexy	..	..	+							
		2 mos.	Hesitancy	+									
		Indeterminable	Intention tremor, right	+									
S. S.	1 yr.	2 yrs.	Spastic gait*	..	+	..	..	.....	....	0	0	5	19
		2 yrs.	Diplopia*	..	..	+							
		2 yrs.	Vertigo*	..	..	+							
		Indeterminable	Frequency	..	..	+							
		Indeterminable	Intention tremor, right and left*	..	..	+							
W. A. (t)	1½ yrs.	4 mos.	Hypesthesia of hands and feet	4 +	..	..	..	.....	....	+ Teacher	+	3	In twenties
		2 yrs.	Blurred vision	..	+								
		1 yr., 6 mos.	Hesitancy	..	..	..	+						

the patients except two (J. P. F., who was treated by Dr. George Hyslop, and F. G., a patient of Dr. Gerald Parker).

Not included in the series are three other cases in which the diagnosis was doubtful, but in which the patient improved under treatment, and two cases in which the patient was free from symptoms when treatment was started and has remained so.

The symptomatic status of the various patients, as recorded in table 1, depends not only on the patient's report but also on the objective examination of all patients, except those living at great distances. Opportunity for complete reexamination at a late date in the course of treatment presented itself in about half of the cases. (The remain-

Symptom	Date of Onset	Date of Remission	Character of Symptom	Previous Treatment	Date and Effect of Treatment
1st Symptom					
2nd Symptom					
3rd Symptom					
4th Symptom					
5th Symptom					

Fig. 1.—History blanks for use in cases of multiple sclerosis.

der of the patients either live far away or terminated treatment without reporting for a complete reexamination.) Among those completely reexamined the following points were noted: Abdominal reflexes previously absent returned in seven instances; usually this return affected only one or two of the reflexes, although twice it involved all four reflexes. The new reflexes were brisk in only one instance. The deep reflexes and the Babinski sign rarely showed any change. Nystagmus disappeared occasionally. No definite alterations in temporal pallor were detected. In addition, patients have been required to write their names and addresses at each visit. India ink has always been employed, and each patient has had his own pen. Figure 2 illustrates the changes which have occurred in the handwriting.

A summary of the symptomatic outcome is given in table 2.

REGRESSION DURING TREATMENT

Development of New Symptoms (table 1).—All told, seventeen new symptoms, in ten patients, appeared during the course of treatment. Of these, eight, in four patients, disappeared and have not returned up to the present time. This means that six patients now have nine symptoms which were not present when treatment was begun (in one patient [W. S.] there were three new symptoms, of which only one definitely disappeared, and in another [S. S. S.] it was uncertain whether or not the symptom had disappeared). This appears to be a small incidence in a series of forty-nine patients with three hundred

TABLE 2.—*Summary of the Symptomatic Outcome*

Duration of Symptom	Improved	Regressed	Unchanged	Unknown
0 to 6 months	26	1	5	2
6 to 12 months	20	3	11	0
12 to 18 months	33	5	3	0
18 to 24 months	16	2	4	1
Recent, undetermined	18	3	5	4
2 to 3 years	22	10	16	2
3 to 4 years	12	3	8	0
4 to 5 years	10	2	11	0
5 to 6 years	5	3	4	0
6 to 8 years	1	0	2	0
8 to 10 years	0	0	5	2
10 years or more	1	0	2	2
Long, undetermined	5	3	14	1
Total	169	35	90	14

and eight symptoms. Of the six patients, five have improved in most other respects, and since most of the new symptoms are of minor importance the patients are still much better off than they were at the beginning of the treatment.

Regression of Old Symptoms (tables 1 and 2).—Of the three hundred and eight symptoms suffered when treatment was started, thirty-five (11.3 per cent) have grown worse. These are distributed among fourteen patients, only one of whom is included among the six with permanent new symptoms. Thus, twenty of the forty-nine patients are, in some particular respect, worse than they were when treatment began. The situation is not so bad as it appears at first glance, however. Of the thirty-five separate symptoms which have regressed, twenty-three are in seven patients (seven of them in patient M. N.), and twelve are scattered among seven others. In the latter group of seven the regressions are isolated, and in five they are associated with improvement of other symptoms. As has been stated, the same applies to five of the

six patients with permanent new symptoms. All told, only eight of the forty-nine patients are in worse condition than at the beginning of the treatment; these are B. A., H. W. (deceased), W. S., F. D. (deceased), L. S., J. A., J. C. and M. N. (deceased). (This total does not include K. O., in whom the multiple sclerosis did not regress, but who died of pneumonia.)

DETAILS OF SYMPTOMATIC IMPROVEMENT DURING TREATMENT

Certain aspects of the actual improvements (table 2) should be stressed. In the earlier report [1] it was stated that the bulk of the symptomatic improvements occurred among symptoms of no longer standing than eighteen months. This conclusion has been borne out, with slight modification; about 73 per cent of the symptoms of less than two years' duration have improved; of those of more than two years' duration, only about 44 per cent have improved. For the sake of convenience, symptoms of from one and one-half to two years' duration or less will be alluded to as new and those of longer duration as old. It may be noted that of the thirty-five symptoms which regressed, twenty-four are in the new group; twenty of these are in six of the seven patients who made a general regression.

No difference in the course of the disease was found between males and females nor between various physical and emotional types of person. It was found that one pair of symptoms, frequency and urgency of urination, responded better than others in the course of treatment (in the previous publication on quinine therapy it was stated that there were no differences in the responses of different symptoms). Not only is the proportion of improvements of frequency and urgency unusually great—especially in the older group—but the remissions are, on the whole, earlier and more striking. Possibly quinine has some special action on the bladder or on its nerve supply. Also, the symptom of spasticity of the lower extremities appears to improve less well than any of the others. Dr. Jelliffe has offered the suggestion that quinine may perhaps have a tone-increasing action on striated muscle similar to that of quinidine on heart muscle.

ANALYSIS BY AGES OF PATIENTS AND BY CLINICAL GROUPS

The general statement may be made that striking results were more frequent among the younger than among the older patients. Although a definite differentiation by ages cannot be made, in general the result from this standpoint coincides with that of Gross, as given in his report on the treatment of multiple sclerosis with vaccines,[3] excepting that in

3. Gross, Karl: Jahrb. f. Psychiat. u. Neurol. **42**:19, 1922.

Gross' series the borderline lay at about the age of 40, while in the present group it would have to be placed in the middle thirties.

No real differentiation could be made between the results of treatment in the clinical groups 1 to 5 (table 1), although there is a moderate preponderance of group 3 over group 2 among the patients who had the most striking results. This carries no final connotation, however; the delineation between groups could not be very accurate, and also the number of cases in each group is too small to have statistical value.

ANALYSIS OF INDIVIDUAL PATIENTS

A general view of the present status of the forty-nine patients as individuals strongly indicates that quinine therapy has been helpful. Eight have indeed shown significant symptomatic regression while under treatment. Of these, two (F. D. and M. N.) have died, F. D. of an unknown cause some time after terminating his treatment, and M. N. of infected decubitus ulcers while still under treatment. Another of that group of seven, H. W., who had isolated regression of a single symptom, also died, long after cessation of treatment. Two of the seven patients had improved considerably before regression occurred. One more, K. O., who had no symptomatic regression, died of pneumonia while still taking quinine.

The complete status of three patients (N. G., J. P. F. and F. G.) is insufficiently known.

There are, then, thirty-seven patients who are either better, or no worse, after what has usually been a long period. Table 1 shows how long these periods have been. Twenty patients are free from incapacitating symptoms, and five more are almost so; all of these persons are either working or able to work. None who were able to work prior to the beginning of treatment are now unable to do so. Ten still have symptoms which are definitely incapacitating, and two (H. E. and P. E., under treatment for one and one-half and six months, respectively) are continuously improving, with expectations of eventually being able to resume work. In summary, it may be stated that in twenty-five patients either the condition is in a state of remission or there is definite improvement (or was when treatment was terminated), that in ten patients the condition is arrested, and that two patients appear to be in a state between remission and arrest of the condition. Of those who have had remission or made improvement, only the two already referred to have had regressions; otherwise all the patients with remissions or improvement have so far maintained them.

In the previous publication it was said that the improvement generally commenced from four to six weeks after the institution of treatment. This has continued to be the case. This is one of the facts which points to the effectiveness of the treatment rather than to the

accident of spontaneous remissions, even though the statement applies only to the majority of the cases and not to all. Occasionally improvement has started more promptly, and occasionally less so. Once improvement has commenced, it may continue gradually.

Collateral evidence that quinine is helpful may be seen from the various shocks and strains through which some of the patients have passed without deleterious consequences. R. P. (male) was struck by

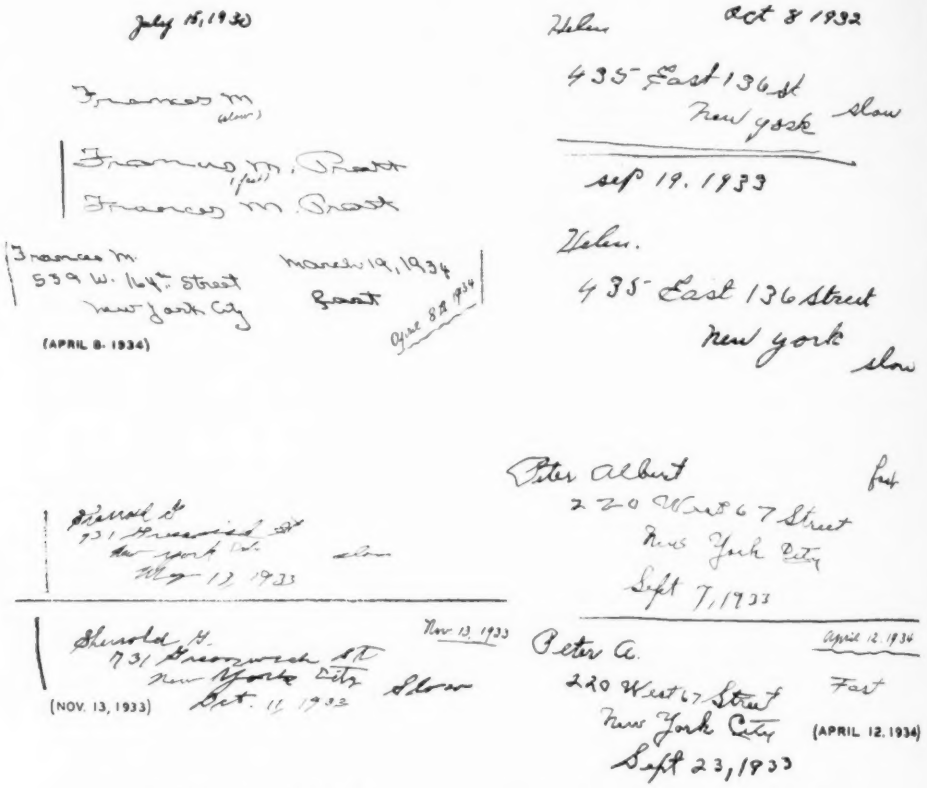

Fig. 2.—Changes which have occurred in the handwriting of four different patients.

a trolley car, and although he escaped with mere bruising the shock was considerable; it did not result in relapse. M. S. (male), caught on the beach during a large fire at Coney Island, had to swim three blocks in the ocean to reach a safe spot. J. M. (male) was thrown off a motor-cycle and bruised; he was unable to walk for fifteen minutes, but showed no effect thereafter. H. E. had an abortion under ether anesthesia, followed by slight general relapse which lasted from ten to fourteen days. R. H. drove (himself) across the continent three times

in a year. W. B. (female) has experienced two prolonged, severe attacks of pyelitis with high fever, and has undergone a series of treatments with high voltage therapy for rapidly growing uterine fibroid tumors. During each of these experiences she suffered a severe relapse of the neurologic symptoms, becoming paralyzed in all four extremities, with incontinence of urine and feces, but each time she returned to her old level after cessation of the insult.

Many patients have experienced colds and grip without neurologic sequelae, although an equal number have suffered relapses under similar circumstances; the latter have all regained their preinfection levels promptly. Also, emotional disturbances, sometimes rather severe, have never produced more than slight, transitory regressions.

GENERAL COMMENT

Numerous factors interfere not only with the success of treatment but also with the opportunity to conduct it. Chief among these is, perhaps, the dissatisfaction of some patients with mere arrest of the condition, or the failure to find relief from a troublesome symptom. Patients are discouraged when the symptoms which disturb them most are among the older ones and do not respond as well as more trifling difficulties which may be newer; the treatment of an old paraplegia which does not improve, combined with a newer numbness of one hand which does improve, may interest the physician but serve only to dishearten the patient. Neurotic attitudes have caused some patients to discontinue treatment; in one (S. S. S.) the menses became irregular, and the patient, attributing the change to quinine, chose to stop treatment, although she had experienced one of the most striking remissions in the series. To some, other types of therapy have seemed more promising than quinine. In some cases real failure of the treatment caused discontinuance of it, and in some inability to tolerate quinine made discontinuance necessary. On the whole, however, patients have adhered to the treatment faithfully.

In addition, there is no doubt that the best responses have occurred in patients the total length of whose illness has been short, in those who are in their first attack, in those in whom the progress of the disease has not been rapid and in those whose symptoms are not far advanced when treatment is begun. The more extreme a symptom, the less chance there is for full recovery from it. Even when patients are undergoing regression from a full remission, the results, in general, are less satisfactory than when treatment is given during a first attack. Glial changes have probably remained from the previous episode, impairing the chance of a completeness of improvement which still exists in an initial attack. With each subsequent onslaught the permanent gliosis probably increases, so that less and less remission is possible.

In late stages it is probable that there is a dense gliosis leading to the death of the cells, rather than active multiple sclerosis. A similar explanation may obtain for the fact that in fulminating, rapidly progressing cases, treatment is apt to be less successful than in slowly advancing ones, even though the attack is an initial one; when the progress is rapid, gliosis is probably equally rapid. None the less, treatment should not be omitted, even in the more discouraging cases, since partial improvement or even mere arrest is, of course, better than nothing, although the patients may not see the matter in that light.

The technic of administration of quinine has been reviewed previously.[4] There have been no major changes in it since the publication of those reports. In brief, the principle is to give, orally, as much quinine hydrochloride as is possible without the development of cinchonism. It should be remembered that cinchonism, like any other form of poisoning, may be harmful in cases of multiple sclerosis. General sensitivity to quinine has been the only usual contraindication to its use, although in one case treatment was stopped because of advancing deafness and in another because of increasing blindness. In most cases with visual impairment, blindness has improved, and in one instance an inmate of a home for the blind lost his place there because of visual improvement. No definitely harmful effects have occurred because of quinine poisoning, probably because cinchonism has never been allowed to progress.

Previously it was stated that "according to the hypothesis, quinine should not cure the disease, but should merely depress the activity of the myelinolytic agent. Therefore, the drug should, theoretically, be taken indefinitely." Since then, medication has been omitted over periods of weeks or months in patients who were relatively free from symptoms. These patients (as well as all the others but one [N. G.]) have been kept under frequent observation.

There is still no basis for expecting quinine to do more than inhibit the activity of the disease, and the drug should have nothing to do with the rebuilding of myelin. Any aid to this process might be valuable. The recent publication of Dragomir [5] and, in this country, of Weinberg [2] are of interest in their espousal of the intraspinal injection of lecithin in cases of multiple sclerosis. Although there is no proof that the lecithin is actually utilized by the body in the laying down of myelin, these authors claim good results for the method. Weinberg did combine it with the administration of quinine in his later cases. It may be that the union of the two methods will prove useful,

4. Brickner, Richard M.: The Administration of Quinine Hydrochloride in Multiple Sclerosis, New York State J. Med. **31**:885 (July 15) 1931; footnote 1.

5. Dragomir, Teofil: Cluj. med. **10**:288, 1929.

especially when the simpler procedure of oral administration of quinine is insufficient.

SUMMARY AND CONCLUSIONS

Quinine hydrochloride has been employed for five years in treating patients with multiple sclerosis.

In any therapeutic attack on multiple sclerosis the question of spontaneous remissions is a source of confusion in evaluating the results of treatment.

In the present investigation this phase of the problem has been approach in part by considering not only the clinical improvements made by patients but also the degree to which new symptoms occurred and old ones grew worse while treatment was in progress. In the forty-nine patients reported on—treated from six months to five years—the incidence of these manifestations was of minor degree; a result of this nature appears to be independent of spontaneous remissions.

Also, observation was made of the speed and completeness of recovery from the regressions associated with colds and other illnesses and of the effects of severe exertion and shock. By these criteria the results also appeared to be favorable.

Concerning actual improvement, it was thought that if it usually began within a more or less regular interval after the institution of treatment and that if the newer symptoms improved more rapidly and more completely than the older, the indications would be that the treatment was responsible rather than spontaneous remissions.

By all of these criteria, the evidence supports the view that it is the treatment itself which is effective. It seems difficult to select criteria that will answer the question of remission any better in so capricious a disease as multiple sclerosis. Its chronicity, the much longer duration of some symptoms than of others, the fact that some symptoms represent the late stage scar while others indicate fresh activity of the disease, the progressive damage that may be caused by dense gliosis and the eventual necrosis of the nerve cells, all make it unreasonable to expect such decisive indications of improvement as are shown, for example, by the blood count in cases of pernicious anemia in which liver therapy has been used.

The study has been conducted from the beginning by considering the patients in two different ways: as sick persons and as carriers of a group of symptoms. Only the latter procedure permits separate evaluation of the courses of old and new symptoms, with adequately controlled theoretical analysis of the effects of treatment; the former method, however, is better adapted to assaying the degree of practical usefulness of the therapy.

There were forty-nine patients with a total of three hundred and eight symptoms. The majority (about 73 per cent) of the symptoms of two years' duration or less have improved. There was improvement in about 44 per cent of the symptoms of longer standing. Thirty-five symptoms have regressed during treatment. Only seventeen new symptoms have appeared in the whole group, and of these only nine were permanent.

In twenty-five patients the condition is in a state of remission or they have shown marked improvement and are working or able to work; of these, twenty are free from incapacitating symptoms and five are almost so. None who were able to work prior to treatment are now incompetent to do so. The condition in ten is apparently in a state of arrest, though the patients are incapacitated to a greater or lesser degree; two appear to be emerging from this state into one of improvement. Eight are in worse condition than they were prior to treatment. Of these, three have died. An additional patient, in whom regression of the multiple sclerosis did not occur, died of pneumonia. All but two of those who have experienced remissions or improvements have maintained them.

The dosage of quinine hydrochloride must be determined separately for each patient. Cinchonism should not be permitted, since it has the same deleterious influence on multiple sclerosis as have other forms of poisoning. In general, as much quinine should be given as is possible without cinchonism. The administration of quinine must be continued indefinitely. The medication is given orally, in the form of hydrochloride of quinine.

The detailed employment of therapy is outlined in other communications.[4]

The statement seems justified that quinine is really beneficial in the treatment of multiple sclerosis. When improvement cannot be obtained, it is worth while to try to arrest the process. The best responses have occurred in patients the total length of whose illness has been short, in patients who are in their initial attack, in those in whom the progress of the disease has not been rapid and in those whose symptoms are not far advanced when treatment is begun.

Quinine hydrochloride therapy should be tried over a long period, however discouraging the outlook may appear.

SYRINGOMYELIA AND INTRAMEDULLARY TUMOR OF THE SPINAL CORD

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The present state of knowledge of syringomyelia is one of great confusion. The usual clinical conception of the disease is stereotyped and probably inadequate, while its pathology and pathogenesis are poorly understood, in spite of a voluminous literature. There is such conflict of opinion regarding the cause and nature of the disease that the idea is becoming prevalent that several different conditions masquerade under the one name. The frequent association of syringomyelia and intramedullary tumor of the spinal cord has served only to confuse the issue still further. The following study is presented because it seems to offer several unique contributions to the solution of the general problem of syringomyelia and to assist in explaining the association of this disease with intramedullary tumor.

CLINICAL REPORT OF CASE

Orthopedic operation in 1922, on the fifth lumbar vertebra for pain low in the back, without relief, readmission to hospital in 1931, with pain in the neck and lower limbs, nystagmus, complete flaccid paraplegia with atrophy, anesthesia and hyperhidrosis of the lower extremities; removal of part of a soft tumor from the lumbar portion of the spinal cord; syringomyelia and ependymoblastoma at necropsy.

History.—E. R. A., a white woman, aged 24, who had been married for five years and had a healthy child 3 years of age, was first admitted to the service of Dr. E. W. Ryerson at St. Luke's Hospital on Nov. 3, 1922. She complained of attacks of dull, aching pain in the lower part of the back before arising each morning for about a year and a half. She had had repeated attacks, with intervals of relative freedom which became progressively shorter. At first she could obtain relief by getting up and moving around, but six months after the onset this maneuver would bring on sharp shooting pains which radiated down the legs. Eventually she suffered constantly from one or the other of these types of pain, with only slight relief from various changes of posture. During this year and a half she had slept poorly and had lost 16 pounds (7.3 Kg.) in weight.

First Admission.—Examination, which did not include a neurologic study, revealed nothing objectively abnormal, but bending forward, backward or to either

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From the departments of Neurology and Pathology, St. Luke's Hospital.

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side produced a sharp pain which radiated down both legs to the feet. Roentgen examination of the spine showed an enlarged left transverse process of the fifth lumbar vertebra.

At operation on November 4, this transverse process was partially removed, and within ten days the patient was able to sit up in a chair, although she was still suffering from pain. She was discharged on November 21, somewhat improved.

Second Admission.—The patient reentered the hospital nine years later, on Sept. 9, 1931, having borne three normal children in the interim. She had continued to suffer from the same pains, and in addition some pain in the back of the neck had been present for three or four years. Unsteadiness of gait had appeared at about the same time but had disappeared and returned at intervals. Sensations like "pins and needles" then occurred in both lower extremities. Walking had been impossible without assistance for the preceding seven months. Two months prior to admission she had become very constipated, with incontinence of both bladder and rectum, and had had some dysuria. During the last nine months she had lost 20 pounds (9.1 Kg.) in weight.

The general examination disclosed nothing abnormal except mild secondary anemia. Neurologic examination by one of us (J. F.) on September 10 revealed: marked general weakness of both legs with considerable atrophy, which was more severe on the left; marked lumbar lordosis; pain high in the neck and severe pain in the legs; rectal and urinary incontinence, with a history of retention at times; increased sweating in the lower half of the body; absence of tendon reflexes in the right arm and in both lower extremities; absence of all abdominal and plantar responses; definite "riding breeches" anesthesia to pain, tactile and temperature sense in the region of the third, fourth and fifth sacral dermatomes and the coccygeal area; a patchy disturbance in the fifth lumbar segment and the first and second sacral areas, and nystagmus on lateral gaze. Ophthalmoscopic examination revealed somewhat enlarged veins but no papilledema or redness or pallor of the disks. The patient's speech was rather slow, but not of any special type.

The opinion was expressed that the findings indicated multiple lesions. The definite saddle anesthesia to all types of sensation, and severe pain, without signs referable to the pyramidal tract, spoke against multiple sclerosis. In view of this picture and the total absence of hope of relief by any other means, laminectomy was considered to be justified.

On September 11, a spinal puncture was done through the fourth lumbar interspace, but no fluid was obtained. Puncture in the third space yielded about 10 drops of yellowish, thick fluid. Queckenstedt's procedure produced no rise in the manometer.

Operation.—On September 14, under ether anesthesia, Dr. E. W. Ryerson performed laminectomy between the ninth thoracic and the second lumbar vertebra. A large soft tumor was found inside the dura at about the level of the tenth to the twelfth thoracic vertebra and was partly removed. Little spinal fluid was present, suggesting a block higher up. The patient went into a state of shock and in spite of intravenous and other vigorous treatment died at 11:20 p. m.

PATHOLOGIC REPORT OF CASE

Postmortem examination was allowed only of the spinal cord. No outstanding gross abnormalities were seen on the surface of the cord except in the midlumbar region, where a tumor of fragile tissue, a part of which had been removed, was visible. The meninges were apparently normal except over this tumor, where, as a result of the operation, they were entirely missing. Cross-sections of the

cord at various levels revealed a longitudinally extending central cavity, varying in size and shape, which extended from the first cervical segment to the filum terminale except where the tumor was situated. Around the cavity there was a broad lining of firm tissue which in the preparations fixed in formaldehyde appeared glistening and of the color of ivory, being somewhat lighter in color than normal white matter.

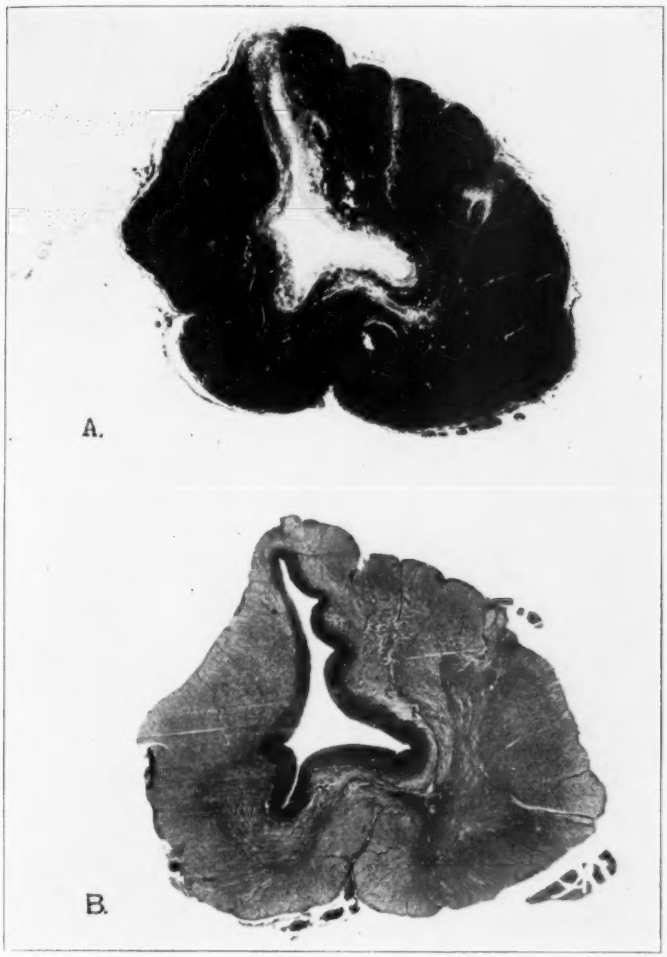

Fig. 1.—*A*, cross-section of the spinal cord in the cervical region (Weigert-Pal's stain). Note the relatively insignificant myelin degeneration. Magnification, × 5. *B*, the same section stained with phosphotungstic acid and hematoxylin. The gliosis lies dorsal to the central canal and extends into the right dorsal and ventral horns. The cavity has no lining save the gliosis. Magnification, × 5.

Microscopic examination was made of preparations from many parts of the cord and from the tumor removed at operation, the usual laboratory methods of staining being used. In addition, Mallory's aniline blue and phosphotungstic acid

and hematoxylin stains were used, and several sections were prepared by the gold sublimate method of Cajal and Davenport's silver technic. At several levels the myelin sheath method of Weigert and Pal was used.

For the most part the cavity or syrinx lay in the region of the median dorsal septum, between the dorsal funiculi and immediately behind the gray commissure (fig. 1). This arrangement was seen in its simplest form in the lower thoracic segments, where the cavity, in cross-section, was merely a dorsoventrally direct slit (fig. 2). Various complications of this simple slitlike cavity occurred in other portions of the cord. In the whole cervical and upper thoracic segments there was a dorsolateral extension which occupied practically the whole of the right dorsal horn, including the major portion of Clarke's column (fig. 1). In the upper cervical segments another arm of the cavity extended less widely into the ventral horn.

In the midlumbar region (fig. 7) the syrinx had been replaced by the tumor, and only the ventral third of the cord persisted as a cup-shaped crescent which

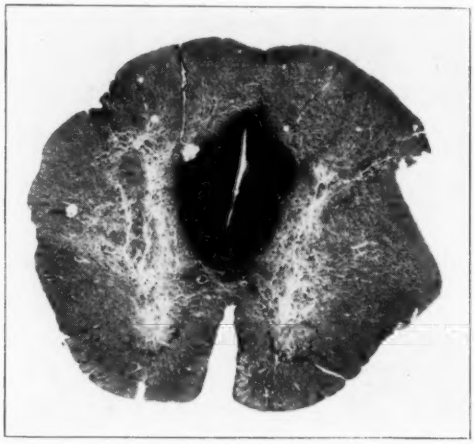

Fig. 2.—Cross-section from the midthoracic region of the spinal cord. The gliosis is restricted to the central portion of the dorsal columns. Some degeneration has occurred in the surrounding white matter. Phosphotungstic acid and hematoxylin; × 5.

held the tumor in its dorsal concavity. At this level only the ventralmost tips of the ventral horns were seen in their normal relationships.

Caudad to the tumor the cavity reappeared, but in this location the pathologic relationships were highly complicated in a manner to be described later. The conditions again became simple in the filum terminale (fig. 12), where a central syrinx was present, with the interesting addition, however, that here the cavity remained open to the subarachnoid space in the median dorsal line, a condition closely resembling that in the primitive neural tube before its closure.

For convenience in histologic analysis, the detailed description of the cord will be divided into three parts: (1) conditions cephalad to the tumor (first cervical to first lumbar segment, inclusive); (2) conditions in the tumor itself, and (3) conditions caudad to the tumor (fifth lumbar segment to the filum terminale).

APPEARANCE CEPHALAD TO THE TUMOR

The Syringomyelic Gliosis.—Cephalad to the tumor the syrinx was lined everywhere by a broad band of tissue which took no stain by the myelin sheath method of Weigert and Pal (fig. 1 *A*) but which in the preparations stained with phosphotungstic acid and hematoxylin was a rich blue (fig. 1 *B*). This tissue was essentially a dense gliosis consisting of a heavy network of glia fibrils, among which lay relatively few glia cells. Some of these cells were ependymal spongioblasts with one process directed peripherally and another centrally, the latter terminating on an end-plate at the border of the lumen (figs. 3 and 4). These spongioblasts gave rise to long fibrils which occasionally branched dichotomously. The other cells of this tissue were adult astrocytes taking the Cajal gold sublimate or the Davenport silver stain, but they were often irregular and distorted and the tissue in general was much more heavily fibrillar than one sees in astrocytomas. The fibrils of this glial network were, furthermore, in general thicker and less delicate and the meshes of the network much more closely woven than is the case in any of the gliomas or in the ordinary reactive or "secondary" gliosis in the spinal cord.

Some of the cells, especially near the lumen of the cavity, were swollen and rounded and were filled with fat globules which stained well with scarlet red. Some were definite gitter cells, while others had lost their nuclei entirely (fig. 5). This appearance suggested that the lumen may have arisen, at least in part, by a process of degeneration in the central portions of the gliotic mass. The lumen presented no ependymal or other organized lining except the frayed edge of the gliosis.

There was increased vascularity in the outer layers of the gliosis where the glial network merged with the surrounding tissues of the spinal cord. The walls of the vessels were often considerably thickened, in some cases almost to the point of obliteration. The central portions of the gliosis, on the contrary, were sparsely supplied with blood vessels, a condition which may explain the central degeneration and formation of the lumen. The glial network was thickened about the vessels, forming in effect a dense perivascular glial membrane. Many of the glia cells contributed so-called "sucker feet" to this membrane. The gliosis thus behaved toward the walls of the vessels after the fashion of normal glia.

No areas of necrosis were found in any of the gliotic tissue cephalad to the tumor except, as described, close to the lumen of the syrinx. There were no areas of "homogenization," a term used by Petrén [1] to describe portions of the glial feltwork which had undergone degeneration and appeared "homogeneous." Hassin [2] made a careful study of such areas in his case and described them as consisting of degenerating glia with partially preserved myelinated fibers. In the areas of gliosis in our case no myelinated fibers could be found except at the periphery, where the glia network was not so dense. Likewise no collagenous scar tissue was found in any part of the cord cephalad to the tumor, and there was no mesoblastic structure except that already described in the walls of the blood vessels. This is in marked contrast to the condition found caudad to the tumor, which will be described later.

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1. Petrén, Karl: Beiträge zur pathologischen Anatomie und zur Pathogenese der Syringomyelie und der Syringobulbie, Virchows Arch. f. path. Anat. **196**:377, 1909.

2. Hassin, G. B.: A Contribution to the Histopathology and Histogenesis of Syringomyelia, Arch. Neurol. & Psychiat. **3**:130 (Feb.) 1920.

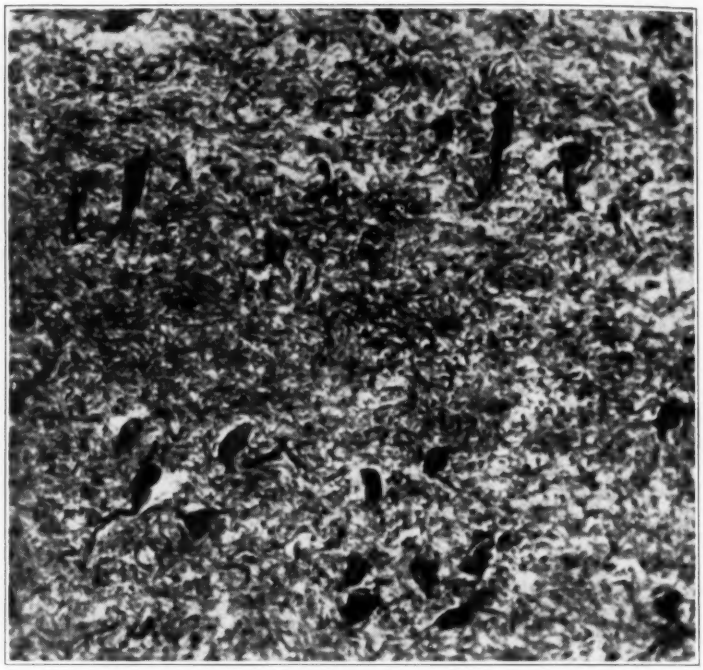

Fig. 3.—The syringomyelic (primary ependymal) gliosis. The heavy mass of glial fibrils, for the most part cut in cross-section, is well illustrated. The cells with stained cytoplasm resemble spongioblasts and give rise to heavy fibrils. The naked nuclei represent astrocytes. Phosphotungstic acid and hematoxylin; × 630.

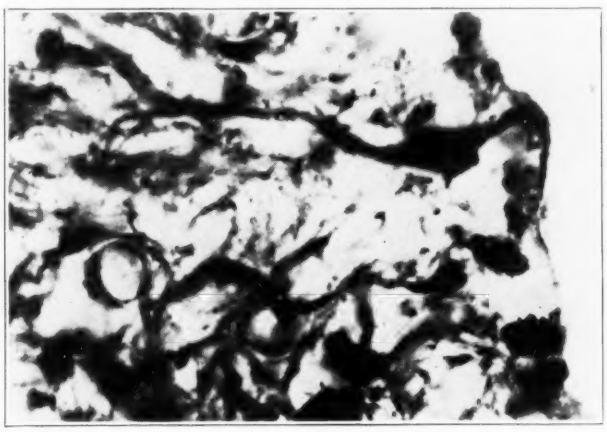

Fig. 4.—An ependymal spongioblast from the gliotic tissue stained by Davenport's silver method. The proximal process terminates in an end-plate which borders the lumen of the syrinx. Reduced from a magnification of × 920.

Changes in the Cord Surrounding the Syringomyelic Ring.—In the cervical region no marked changes were noted in either the white or the gray matter surrounding the syringomyelic gliosis. The fibrillary astrocytes near the gliosis showed a slight reactive proliferation. The main gliotic process, however, shaded off so gradually into the normal glial structure of the white matter of the cord that it was difficult to draw the exact boundary line between the two. In the mid-dorsal region (fig. 6) great numbers of swollen, rounded, often vacuolated and fat-filled glia cells were seen in the surrounding white matter. Many of these

Fig. 5.—Fat-containing cells in the gliosis, adjoining the lumen. Many of these are recognizable as astrocytes packed with globules of fat. Others seem to be ordinary fat granule cells, perhaps of astrocytic origin. Phosphotungstic acid and hematoxylin; × 920.

cells had apparently lost their nuclei, while a few were binucleated. They were recognized as *gemästete* glia cells in a stage of degeneration following proliferation. Fat granule (gitter) cells were seen occasionally in this peripheral area around the gliotic tissue. The ganglion cells of the dorsal and ventral horns, where not actually destroyed by the gliosis, were normal in appearance. Preparations stained by the Weigert-Pal method demonstrated relatively little secondary degeneration in the white matter (fig. 1*A*). The dorsal columns, and especially the fasciculi

gracilis, were slightly less rich in myelin than was the remainder of the white matter, but no striking areas of demyelinization were in evidence.

Cephalad to the tumor the ependymal cells of the central canal region were at no point involved in the gliosis. Only rarely was a formed central canal found; for the most part the ependymal cells seemed to have lost their polarity and were scattered widely to either side, sometimes almost to the extremities of the commissure. These ependymal cells lay in the meshes of the glia in the commissure and were recognized by their epithelioid morphology. However, it was often difficult to say whether a given cell was ependymal or glial, as stained by the phosphotungstic acid-hematoxylin method, since many apparently epithelioid cells were polar and gave rise to processes.

Fig. 6.—Swollen astrocytes in the edge of the gliotic tissue, and in the adjoining white matter. Phosphotungstic acid and hematoxylin; × 234.

APPEARANCE AT THE LEVEL OF THE TUMOR

The tumor lay between the first and the fifth lumbar segment (fig. 7). Here the cord was entirely destroyed, except in its ventral third, where the median ventral fissure and the tips of the ventral horns were recognizable and retained their normal relations. This remaining portion of the cord was cup-shaped and contained the tumor in its dorsal concavity, while the tumor itself had been partially excavated on its dorsal aspect at the time of operation.

Lying between the tumor proper and this remaining ventral portion of the cord was a thin band of gliotic tissue identical with the syringomyelic gliosis seen at other levels of the cord. In the interstices of this gliosis lay large numbers of ependymal cells, but it was again often impossible to say whether a given cell was

ependymal or glial, since many epithelioid cells possessed fiber-bearing processes. As one passed dorsally from this band of tissue toward the center of the tumor, the fibril-producing glia became less numerous and the ependymal cells more numerous, but in places the gliotic tissue involved the tumor itself to a considerable depth.

Structure of the Tumor: In general, the tumor was highly cellular and presented a veritable conglomeration of ependymal and glial elements, often in the most intimate association. The majority of the cells were ependymal in type, with a rather abundant, faintly eosinophilic cytoplasm. The nuclei were ovoid or spherical, and contained a clear colorless nuclear plasma and scattered chromatin granules which tended to array themselves along the nuclear membrane. In many places the cells seemed to unite to form a multinucleated syncytial mass. For the

Fig. 7.—Cross-section of the cord and tumor at the third lumbar segment. Part of the tumor had been removed at operation. Phosphotungstic acid and hematoxylin; × 5.

most part, however, these cells of ependymal type were laid down in broad sheets without architectural peculiarities except their tendency to arrange themselves in a palisade formation about the blood vessels. In a few places some of the cells formed characteristic ependymal tubules with a small, circular well defined lumen (fig. 8). Blepharoplasts appeared in these cells near the lumen. In other locations the cells were arranged in a long cuboid or columnar layer, and often glial fibrils could be seen arising from the inner poles of these cells to form a tangled mass or to stream in wavy parallel lines to be inserted on the adventitia of blood vessels (fig. 9).

In contrast to this morphology, many parts of the tumor presented a considerable amount of predominantly fibrillary glial tissue. This was for the most part made up of astrocytes, but it was often possible to recognize unipolar or bipolar

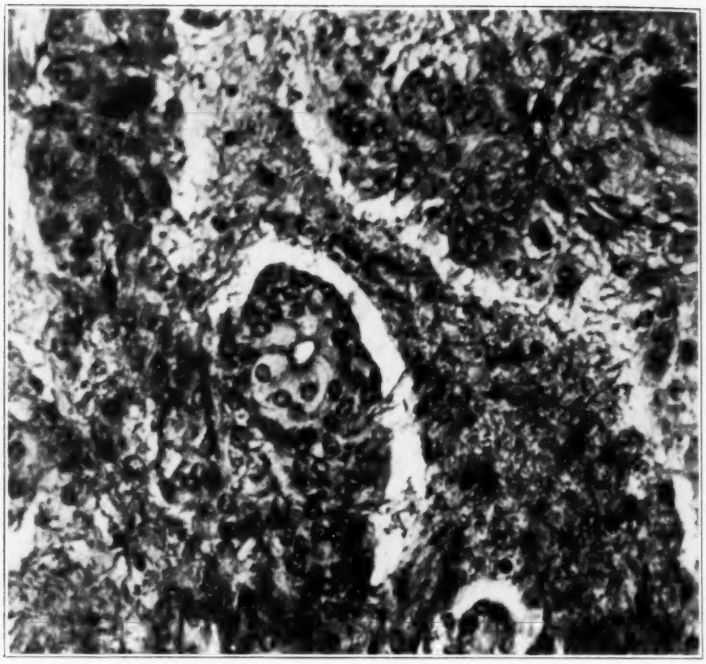

Fig. 8.—Epithelial elements in the tumor, with one tubule. To the right of the tubule appears tissue similar to the syringomyelic gliosis. Phosphotungstic acid and hematoxylin; × 198.

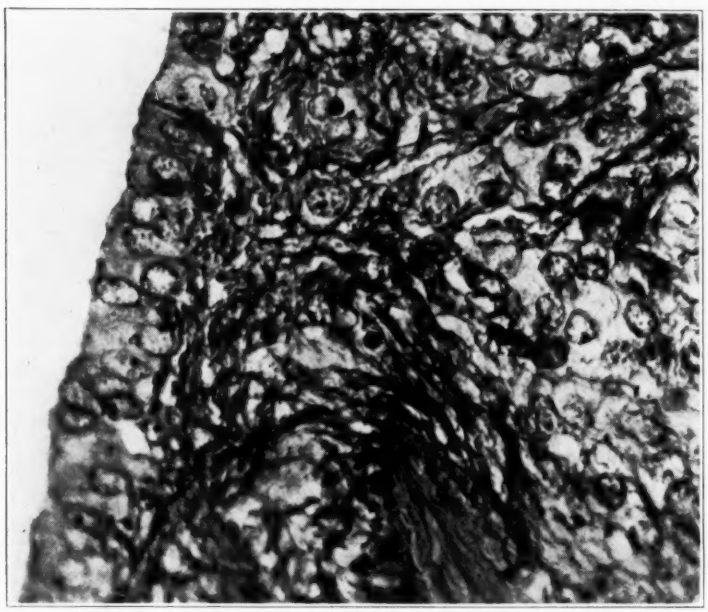

Fig. 9.—Ependymal epithelial layer in the tumor. From the inner ends of these cells arise glia fibrils which pass as vascular processes to a blood vessel. Many such areas were found in this specimen, which was part of the tissue removed at operation. Phosphotungstic acid and hematoxylin; × 630.

forms giving rise to fibrils and suggesting fibril-bearing spongioblasts. Occasionally a large group of delicate fibrils lay in parallel wavy bundles, as seen in preparations stained with the phosphotungstic acid and hematoxylin. It was impossible not to recognize the close similarity between these heavily gliotic areas in the tumor and the primary gliosis of the syringomyelia. So closely interrelated were the glial and epithelial elements in the tumor that it was difficult to discover any predominantly epithelial areas which did not exhibit a delicate fibrillary network between the epithelial cells. Many other cells could be found which were apparently ependymal in type but which were elongated and gave rise to glia fibrils. These cells appeared to be intermediate morphologically between the ependymal and the glial type, and many of them were indistinguishable from spongioblasts.

It was thus possible to demonstrate in this tumor numerous intermediate gradations from the typical gliosis of syringomyelia, with its fibrillary astrocytes and ependymal spongioblasts, to cells of a characteristic mature ependymal morphology.

Mesodermal connective tissue was strikingly rare in the tumor. The blood vessels, which were rather numerous, usually exhibited somewhat thickened walls, and often a tangled glial network surrounded the vessel, outside the adventitia. In one of the operative specimens areas occurred which contained heavy bands of collagenous connective tissue, surrounded by an intimate mixture of ependymal and immature glia cells. The latter lay in an axis perpendicular to the connective tissue, to which they gave off large numbers of glia fibrils.

The question whether the tumor had invaded the meninges cannot be answered in this case, since the whole dorsal portion of the tumor, with the meninges, had been removed or destroyed at the time of operation. Certainly the whole dorsal two thirds of the cord appeared to have been destroyed by the tumor growth.

APPEARANCE CAUDAD TO THE TUMOR

Below the tumor, for instance, in the fifth lumbar segment (fig. 10), the typical gliotic ring, so characteristic of the areas above the tumor, was again seen, but it was highly complicated by the introduction of additional features. Here the normal topography of the cord was destroyed; only the median ventral fissure could be identified, and none of the gray matter was recognizable. The gliotic ring extended practically to the pia on all sides except in the ventral columns, where the white matter had degenerated and where swollen, ameboid glia cells were occasionally found. In the left dorsal part of the cord the gliosis appeared as an irregular, heavily stained crescent (fig. 10). This gliosis was like that already described for the portions of the cord cephalad to the tumor except that the fibrillary network was more dense, the nuclei were fewer, and the immature, spongioblast-like forms were infrequently encountered. It was thus apparently older and more quiescent, and the cells were of a mature astrocytic type.

The remainder of the gliotic ring at this level presented many evidences of degeneration, a condition not present in the portions of the cord cephalad to the tumor. The fibrils did not take the fibrillar stains well; many of the nuclei were shrunken, dark-staining and pyknotic, while others were hazy, vague and broken down. The gliosis in these areas was on the whole less compact and firm, but it was histologically easily recognized.

In the center of this ring of gliotic tissue lay the cavity, which was irregular, stellate and rather complicated in form. It was lined by highly vascular collagenous connective tissue and in places by laminated fibrin and erythrocytes. Where the surrounding glial ring had undergone extensive degeneration, the connective tissue had invaded and replaced it, thus producing an intimate mixture of fibrous and

glial tissue. In the interstices of this central, netlike mixture of gliosis and sclerosis were seen large numbers of cells which were rather rich in cytoplasm and often multinucleated. In morphology and staining qualities these cells were identical with those of the tumor, and their presence here undoubtedly represented the lower extension of the tumor. A few pigment-bearing phagocytic cells could also be found in this area.

In the segments still more caudally situated there was a gradual decrease in the amount of collagenous connective tissue present in the center of the gliotic ring and a rapid disappearance of the tumor cells. In the lower sacral segments the picture approached closely that obtaining in the cervical and thoracic segments. Here the syringomyelic process was largely restricted to the portions of the cord dorsal to the median ventral fissure. Except for the dorsalmost sector of the syrinx, heavy gliotic tissue composed the whole syringomyelic ring. Dorsally, a

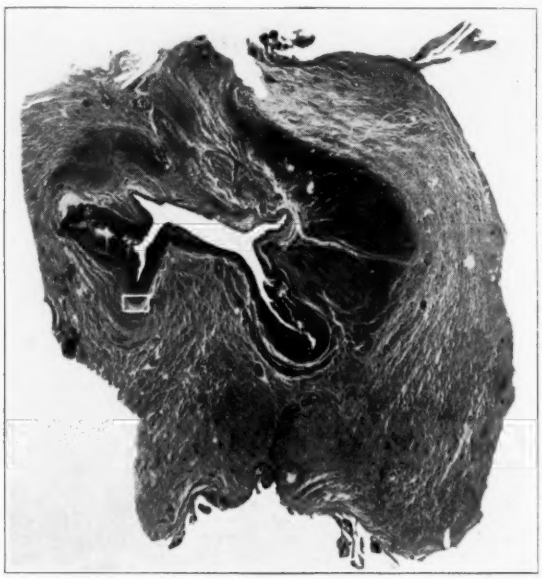

Fig 10.—Cross-section of the fifth lumbar segment of the cord, immediately below the tumor. The normal topography has been destroyed, and only the median ventral fissure can be identified. The cavity contains some red blood cells and is lined by a collagenous connective tissue layer. Immediately outside this layer many tumor cells persisting from higher levels are found, while still farther out lies the syringomyelic gliosis, which is especially well marked in the dorsal portions of the section.

small sector of the gliosis had undergone considerable degeneration and had been largely replaced by connective tissue. Ependymal cells in increased numbers and quite widely scattered were seen in the central canal region, but no canal had been formed here. These ependymal cells were lying loosely in the meshes of the pathologic glial tissue which encroached on their position. At this level also the lumen of the syrinx was lined no longer by connective tissue but again by the gliosis itself. The gliosis was highly degenerated in the portions adjacent to the lumen. Here pyknotic or entirely broken-down glia cells were seen (fig. 11),

Fig. 11.—Degenerating syringomyelic (primary ependymal) gliosis in the third sacral segment. This is a much more acute degeneration than that seen in figure 5. Phosphotungstic acid and hematoxylin; × 234.

Fig. 12.—Cross-section of the filum terminale. At this level the medullary groove has not completely closed, and the lumen is lined by the primary ependymal gliosis of syringomyelia. Phosphotungstic acid and hematoxylin; × 5.

and a few cells were large and stained heavily by the phosphotungstic acid method. Some of these cells were composed of dark, spherical globules, as though they had broken down, leaving only black droplets. Fibrils were seen also which were heavy, club-shaped and blunt and which also stained strongly. These suggested the degenerative forms of glia fibrils described by Rosenthal [3] and sometimes known as "Rosenthal fibers." Portions of white matter left relatively intact by the gliosis were in a degenerated condition, and swollen, ameboid or *gemästete* glia forms were common. No ganglion cells could be identified in these lower sacral segments.

A most interesting condition obtained in the filum terminale (fig. 12). Here the syringomyelic process was again entirely a gliotic one, and the lumen of the cavity was bounded only by gliosis. The ring was not complete, however, but presented a dorsal gap where the cavity communicated with the subarachnoid space outside. In this section the exact gross appearance of the primitive medullary tube was reproduced, but neither medullary epithelium as such nor any form of ependymal tissue was found.

COMMENT

Clinical Aspects.—From a clinical standpoint it was not possible to make a diagnosis of syringomyelia in this case. Although the onset of symptoms can be placed as far back as ten years before death, the conventional clinical evidences of syringomyelia were lacking. The patient eventually presented evidence of a tumor of the spinal cord and not of syringomyelia, although the presence of more than one neurologic lesion was recognized.

This dearth of evidence for a complete diagnosis is explained by the location of the syrinx in a relatively "silent" area of the cord throughout most of its extent. Above the first lumbar segment the lesion lay for the most part in or near the median dorsal septum, leaving even the dorsal columns relatively intact. The involvement of the right dorsal horn in the lower cervical segments explains the absence of tendon reflexes in the right arm, and the almost complete escape of the white commissure explains the absence of sensory changes above the level of the tumor. With these relationships in mind it is easily understood that an entirely symptomless syringomyelia not only is possible but in all likelihood not infrequently occurs and is, of course, clinically not recognized. Such subclinical forms have been recognized pathologically for many years and were described by Schlesinger [4] and others as occurring both in children and in adults.

These considerations also warn against the rather current conception of syringomyelia which makes dissociation of pain and temperature from tactile sense a requirement for its diagnosis. Since the white commissure, bearing the decussating spinothalamic fibers, may not be involved, while

3. Rosenthal, W.: Ueber eine eigenthümliche, mit Syringomyelie complicierte Geschwulst des Rückenmarks, Beitr. z. path. Anat. u. z. allg. Path. **23**:111, 1898.

4. Schlesinger, Hermann: Die Syringomyelie, ed. 2, Leipzig, Franz Deuticke, 1902.

the dorsal, or even ventral, gray masses are severely affected, one may have almost any combination of sensory and motor disturbances. It appears to us that the bizarre and irregular nature of the anesthesias should be considered more important than the pain-temperature dissociation. Sensory changes may be practically absent, as was illustrated by a case we recently observed in the Cook County Hospital. In this patient Horner's syndrome, scoliosis, Charcot's arthropathy, marked atrophy of the hands and arms and moderate cyanosis, with slight atrophy of the legs and bilateral signs of pyramidal tract disease, rendered the diagnosis of syringomyelia almost obligatory, even without the two small patches of hypesthesia for temperature and pain which could be demonstrated. Another patient suffered from chronic trophic changes with ulceration of all the fingers and toes and presented no sensory changes except loss of sensibility to cold in the sacral dermatomes.

The association of syringomyelia with other malformations not connected with the central nervous system will be more fully discussed later in another connection. Suffice it to say here that the occurrence of spina bifida occulta, hydrocephalus, embryologic malformations of the vertebrae and other developmental anomalies, with or without vague and otherwise inexplicable neurologic findings, such as isolated absence of reflexes, etc., should lead one to suspect, although one cannot prove, the presence of a subclinical form of syringomyelia. The infrequency with which the spinal cord is removed and examined at necropsy in non-neurologic cases unquestionably leaves many of these cases unrecognized.

Pathologic Aspects.—The process at work in the production of syringomyelia in our case is obviously one of glial proliferation, located predominantly in the region of the median dorsal septum. The cellular elements in the tissue are mature fibrillary astrocytes and immature ependymal spongioblasts. The fibril-forming propensity of the tissue is outstanding. We have used the term gliosis in referring to this tissue, but since it is blastomatous in nature it must be rigidly separated from the gliosis which is secondary to the destruction of nerve parenchyma. The fibrils of this tissue are, furthermore, heavier and coarser than those in secondary gliosis. There are also definite differences between this gliosis and any form of glioma with which we are familiar, although it resembles the fibrillary astrocytoma more closely than any other. It is much more heavily and richly fibrillary than even the astrocytomas, while the ependymal spongioblasts it contains produce a wealth of strong fibrils not seen in the polar spongioblastomas. Furthermore, none of the gliomas produce so normal and orderly a perivascular glial membrane as does this gliosis. Finally, its occurrence throughout the whole length of the cord in the region of the median dorsal septum is a feature not seen in any of the gliomas.

The unique characteristics of this tissue make it easily recognizable whenever seen in the preparations stained with phosphotungstic acid and hematoxylin. Instead of the term "primary central gliosis" which has long been applied to it, we propose the term *primary ependymal gliosis*. This name distinguishes the tissue from both the gliomas and the secondary gliosis and indicates the ependymal origin of its constituent glia.

The tumor which lay in the lumbar segments of the cord was a typical ependymoblastoma. There were, however, many areas in the tumor which were strikingly similar to the primary ependymal gliosis of the syringomyelia. It was as if the ependymoblastoma had developed in the preexisting syringomyelia. The association of these two types of tissue at once appears to be more than a mere coincidence if the embryologic derivation of their constituent cells is recalled. The germinal cells of the primitive ependymal layer give rise to ependymal spongioblasts which in turn differentiate on the one hand into adult ependyma and on the other hand into adult astrocytes. The primary ependymal gliosis of syringomyelia is thus a tissue composed of ependymal spongioblasts and their descendant astrocytes, while the tumor is a tissue composed of ependymal spongioblasts and their other descendants, the immature ependymal cells. It should therefore be clear that in our case the syringomyelia and the ependymoblastoma were only slightly different manifestations of the same proliferative process.

REVIEW OF THE LITERATURE

The enormous literature on syringomyelia cannot be summarized here. The classic monograph written by Schlesinger [4] in 1902 serves as the best introduction to the subject. This author credited Ollivier d'Angers with coining the name "syringomyelia" and attributing the disease to an embryologic malformation as early as 1824. Since that date, many other explanations have been suggested. The rôle of trauma has often been discussed and has in recent years been defended by Tannenberg [5] in spite of its obvious inadequacy and the fact that the pathologic process of known trauma to the cord is at variance with that of syringomyelia. A history of trauma is furthermore often lacking. Infection has been suggested many times, as by Joffroy and Achard [6] and recently by Levaditi, Lépine and Schoen,[7] although evidences of

5. Tannenberg, J.: Ueber die Pathogenese der Syringomyelie, zugleich ein Beitrag zum Vorkommen von Capillarhämangiomen im Rückenmark, Ztschr. f. d. ges. Neurol. u. Psychiat. **92**:119, 1924.

6. Joffroy, A., and Achard: De la myélite cavitaire, Arch. de physiol. **10**:437, 1887.

7. Levaditi, C.; Lépine, P., and Schoen, R.: Contribution expérimentale à l'étude étiologique de la syringomyélie, Bull. Acad. de méd., Paris **101**:669, 1929.

infection are so often absent, as in our case. Others have supposed that vascular or lymphatic disturbances in the neighborhood of tumors were responsible in spite of the fact that many cases of syringomyelia are not associated with tumors. There is a frequent tendency today to say that syringomyelia is not a nosologic entity [8] but that any of the preceding factors may at times be responsible. Such a theory only confuses the issue and represents a form of pathologic opportunism. Without attempting to explain all instances of cavitation of the spinal cord on a single basis, it seems that the great majority of well reported cases must on pathologic grounds be grouped together.

Little of importance was added to the developmental theory of syringomyelia after its proposal by Ollivier d'Angers until Gerlach,[9] in 1894, reported an important case in which a teratoma lay in a syringomyelic process composed of gliosis and connective tissue. The connective tissue in the cavity of the syringomyelia was a direct continuation of that in the teratoma, and Gerlach drew the conclusion that the syringomyelia as well as the teratoma must be due to the same process of tissue displacement, or *Keimverlagerung*. In 1920 Bielschowsky and Unger [10] reported a closely similar case and supported Gerlach's developmental theory with much additional evidence. Further support was given by Henneberg and Koch.[11]

According to this embryologic conception, syringomyelia is a condition depending primarily on an inadequate and improper fusion of the two folds of the primitive medullary groove. This improper fusion disturbs the position and arrangement of the germinal cells which line the medullary groove and are destined to give rise to both ependyma and glia. Such a process may result in a simple hydromyelia. It may result, on the other hand, in an anatomic malformation of the median dorsal septum, with a consequent excessive proliferation of the glia in that region, with or without formation of a secondary cavity. During the attempted but only partially successful fusion of the medullary folds, mesoblastic elements originally destined to form the pia-arachnoid may descend into the median dorsal septum and come to line the cavity and to proliferate there, forming increased amounts of connective tissue and

8. Kirch, Engen: Ueber die pathogenetischen Beziehungen zwischen Rückenmarksgeschwülsten und Syringomyelie, Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:231, 1928.

9. Gerlach, W.: Ein Fall von kongenitaler Syringomyelie mit intramedullarer Teratombildung, Deutsche Ztschr. f. Nervenh. **5**: 275, 1894.

10. Bielschowsky, Max and Unger, Ernst: Syringomyelie mit Teratom- und extramedullarer Blastombildung, J. f. Psychol. u. Neurol. **25**:173, 1920.

11. Henneberg, R., and Koch, Max: Zur Pathogenese der Syringomyelie und ueber Hämatomyelie bei Syringomyelie, Monatschr. f. Psychiat. u. Neurol. **54**:117, 1923.

blood vessels in the spinal cord. A further result of this combination of malformation and proliferation may be the drawing in of dermal elements and the formation of teratomas.

There is a good deal of evidence in favor of this conception of syringomyelia, aside from the work of Gerlach and Bielschowsky and Unger. For instance, Schlesinger [4] was able to demonstrate an unbroken series of transitional cases from developmental malformation of the central canal to fully developed gliotic syringomyelia and could not delineate the one sharply from the other.

The recently emphasized familial tendency of syringomyelia suggests the same developmental factor. Bruns [12] in 1903, Clark and Groves,[13] Kino,[14] Guillain and Thévenard [15] and Wagner [16] have all reported cases of familial or hereditary syringomyelia, and Ostertag [17] described a family of rabbits, all descended from the same animal, which exhibited both clinical evidences of syringomyelia and pathologically a progressive gliosis in the median dorsal septum, with or without cavitation, a condition highly similar to that seen in cases of syringomyelia in human beings.

The association of syringomyelia and other admittedly developmental disturbances has been emphasized by many authors. Congenital hydrocephalus has been reported several times in association with syringomyelia. Alpers and Comroe [18] have collected reports of some such instances. A case of Sprengel's deformity with defect of the cervical portion of the spine in association with syringomyelia was recorded by du Toit [19] in 1931, and Critchley recently described a similar case of "Sprengel's deformity with paraplegia." [20] Doctor Loren Avery has

12. Bruns: Ein Fall von familialer symmetrischer Gangrän und Arthropathie an den Füssen, möglicherweise beruhend auf familialer Syringomyelie im Lumbosacralmarke, Neurol. Centralbl. **22**:599, 1903.

13. Clark, J. M., and Groves, E. W. H.: Remarks on Syringomyelia (Sacro-Lumbar Type) Occurring in a Brother and Sister, Brit. M. J. **2**:737, 1909.

14. Kino, F.: Ueber heredo-familiäre Syringomyelie, Ztschr. f. d. ges. Neurol. u. Psychiat. **107**:1, 1927.

15. Guillain, Georges, and Thévenard, A.: Mal perforant plantaire familial. Syringomyélie lumbo-sacrée probable chez deux frères, Ann. de méd. **25**:267, 1929.

16. Wagner, Ingeborg: Beitrag zur familiären lumbo-sacralen Syringomyelie. Monatschr. f. Kinderh. **53**:137, 1932.

17. Ostertag, B.: Weitere Untersuchung ueber die vererbbare Syringomyelie beim Kaninchen, Zentralbl. f. d. ges. Neurol. u. Psychiat. **57**:426, 1930.

18. Alpers, B. J., and Comroe, B. I.: Syringomyelia with Choked Disc, J. Nerv. & Ment. Dis. **73**:577 (June) 1931.

19. du Toit, Felix: A Case of Congenital Elevation of the Scapula (Sprengel's Deformity) with Defect of the Cervical Spine, Associated with Syringomyelia, Brain **54**:421, 1931.

20. Critchley, Macdonald: Sprengel's Deformity with Paraplegia, Brit. J. Surg. **14**:243 (Oct.) 1926.

shown us a fetus which has numerous developmental defects, including the Klippel-Feil syndrome, anencephalia and spina bifida with syringomyelia. The association of spina bifida with syringomyelia has been reported so often that it is difficult to select instances from the wealth of literature on the subject. Excellent articles have been written by Henneberg,[21] Klippel and Feil [22] and Turnbull,[23] the last of whom published an illustration showing the inclusion of mesoblastic tissues in the median dorsal septum of the cord. Woltman [24] has given a good clinical and statistical study of the association of "myelodysplasia" with spina bifida.

TYPES OF SYRINGOMYELIA

That pathologic varieties of syringomyelia exist is evident from a study of the literature. The tendency to gloss the problem over by saying that syringomyelia may be due to many different causes is to be deprecated, and a sincere effort must be made to find some unifying principle running through the majority of cases. In our case we found different variations of the pathologic process at different levels of the cord, which appear to link together several types of the disease as described in the literature. These may be outlined as follows:

Simple Gliotic Type.—This type, which is apparently the simplest form of the disease, was represented in the cervical and thoracic segments and in the filum terminale in our case (figs. 1, 2 and 12). Four mechanisms seem to lead to such a condition.

1. Malformation of the Medial Dorsal Septum: The failure of the neural crests to unite properly produces this malformation, as illustrated in the filum terminale (fig. 12). Here the neural crests remained entirely separated, and the central cavity was in free communication with the subarachnoid space.

2. Glial Proliferation: This change follows and is possibly due to the "dysraphism." The proliferation involves the spongioblastic descendants of the germinal cells and results in the primary ependymal gliosis which was so well seen in the cervical and thoracic segments in our case. This process may include the central canal or occur entirely in the septum (fig. 2).

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21. Henneberg, R.: Rückenmarksbefunde bei Spina bifida, Monatschr. f. Psychiat. u. Neurol. **47**:1, 1920.

22. Klippel, M., and Feil, A.: Syringomyélie et spina bifida combinées, Presse méd. **29**:971 (Dec. 7) 1921.

23. Turnbull, F. A.: Syringomyelic Complications of Spina Bifida, Brain **56**:304, 1933.

24. Woltman, H. W.: Spina Bifida: A Review of 187 Cases, Including Three Associated Cases of Myelodysplasia Without Demonstrable Bony Defect, Minnesota Med. **4**:244 (April) 1921.

3. Vascular Proliferation: The third element in the production of the simple gliotic form of syringomyelia is vascular proliferation. The vessels increase both in number and in the thickness of their walls, and the majority lie in the peripheral portions of the gliosis.

4. Central Degeneration: The next element, central degeneration, is probably dependent on an inadequate and gradually obstructed blood supply in the central areas of the gliosis; it is the final step in this process and leads to cavitation. At times it apparently does not occur. It is also possible that the cavity represents in part the original defect in the formation of the septum. This appeared to be true in the filum terminale in our case.

Degenerative-Sclerotic Type.—In some cases the central degeneration appears to extend to almost all the gliotic tissue, and in these cases a sclerosis by connective tissue supervenes. Such a condition was well illustrated in our case caudad to the tumor (fig. 10), where the gliosis had largely been replaced by collagenous and highly vascular tissue. This picture represents a condition which has been most frequently described in syringomyelia. Petrén [1] described such a case in which almost the whole process had become sclerotic, and many others might be mentioned. The case reported by Hassin [2] was of similar type, and the glia was in such a state of degeneration that he emphasized the degenerative elements in the process at the expense of the proliferative. Petrén was of the opinion that the cases of shorter duration were predominantly gliotic, while those of longer duration presented more and more sclerosis by connective tissue.

The question of the origin of the centrally located connective tissue has been much debated. Some authors, including Petrén, have attributed it to an inflammatory reaction, the connective tissue arising from the walls of the blood vessels. The case of Hassin beautifully demonstrates, however, that the connective tissue may be a pial inclusion. In his illustrations the pia and the collagenous lining of the syringomyelic cavity are continuous through a slit in the dorsal part of the cord. Thus Hassin's contribution lends support to the belief of Gerlach and Bielschowsky and Unger that syringomyelia is primarily a maldevelopment of the median dorsal raphe, through which pial connective tissue may extend into the cord. Turnbull's case [23] represents an excellent example of spina bifida and syringomyelia with massive inclusions of pial tissues in the central cavity. The relative amounts of fibrosis and gliosis in any given case of syringomyelia seem to us to depend in large part on the severity of the developmental failure and the degree to which pial connective tissue elements are included in the medullary tube.

Syringomyelia with Intramedullary Tumor.—The frequency of the association of syringomyelia and intramedullary tumor has long been

noted. Kernohan, Woltman and Adson,[25] in a study of fifty-one cases of intramedullary tumor, made a complete examination of the cord in nine, and found syringomyelia (not cavitation of the tumor) in five (55.5 per cent). The five tumors included two ependymomas, one hemangioblastoma, one medulloblastoma and one oligodendroglioma. Russell,[26] Schuback [27] and others have reported hemangiomas, and Davison [28] an astrocytoma, with associated syringomyelia.

The tumor which coexisted with syringomyelia in our case throws much light on the relationship between these conditions. The tumor was an ependymoblastoma, while the syringomyelic tissue was a primary ependymal gliosis. Both were products of the germinal cells of the medullary plate, the one tending toward the mature ependymal type and the other toward the mature glial (astrocytic) type. Neither was "due" to the other; they were diverging manifestations of the same proliferative process.

The frequency with which other types of tumor are associated with syringomyelia is susceptible of a similar explanation. In the case of astrocytoma and other tumors of the astrocytic series, the relationship is clear; the tumor represents simply a more actively proliferative process in the same glial elements which are responsible for the syringomyelia. The place accorded to oligodendroglioma in this scheme will depend on the final decision as to the origin of the oligodendroglia. In the case of hemangioblastoma, lipoma and teratoma, the neoplastic tissue is no longer ependymal or glial but arises from the mesoblastic or ectodermal tissues which are included heterotopically in the medullary tube at the time of its closure.

The recent tendency to classify syringomyelia itself as a tumor seems to us to gloss over a valuable pathologic distinction. In spite of this the distinction is admittedly largely a matter of slowness of growth and the unique location and nonexpanding nature of the primary ependymal gliosis of syringomyelia. In this we are in at least partial agreement with Jonesco-Sisesti,[29] who concluded that syringomyelia and tumors were at opposite ends of an unbroken series and that intermediate forms could be recognized.

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25. Kernohan, J. W.; Woltman, H. W., and Adson, A. W.: Intramedullary Tumors of the Spinal Cord: A Review of 51 Cases, with an Attempt at Histologic Classification, Arch. Neurol. & Psychiat. **25**:679 (April) 1931.

26. Russell, D. S.: Capillary Haemangioma of Spinal Cord Associated with Syringomyelia, J. Path. & Bact. **35**:103 (Jan.) 1932.

27. Schuback, A.: Ueber die Angiomatosis des Zentralnervensystems (Lindausche Krankheit), Ztschr. f. d. ges. Neurol. u. Psychiat. **110**:359, 1927.

28. Davison, Charles: Intramedullary Neoplasm of the Cord with Hematosyringomyelia, Arch. Neurol. & Psychiat. **26**:873 (Oct.) 1931.

29. Jonesco-Sisesti, N.: Tumeurs médullaires associées à un processus syringomyélique, Paris, Masson & Cie, 1929; La syringobulbie, Paris, Masson & Cie, 1932.

CONCLUSIONS

1. Syringomyelia may exist without producing symptoms, or the symptoms may be so few and slight that a diagnosis is clinically impossible. The presence of a few minor neurologic signs, especially when associated with spina bifida, vertebral anomalies or other developmental abnormalities, should lead one to suspect the presence of syringomyelia.

2. Pathologically, syringomyelia is based on a malformation of the median raphe of the medullary tube, a primary ependymal gliosis centering in this raphe and often implicating the surrounding tissues of the cord, and a tendency to central degeneration of the gliosis. Mesodermal tissues are often involved in the process through their inclusion in the medullary tube.

3. The glia cells of the gliosis arise from the germinal cells of the medullary epithelium, which also produce the ependyma. Thus the germinal cells may give rise to an ependymal neoplasm in one portion of the cord while producing syringomyelia in another portion. The tumor and the syringomyelia are therefore different manifestations of the same proliferative tendency.

4. In the same way, other gliomas may arise in association with syringomyelia, while tumors of mesoblastic or mixed origin, such as teratoma, angioma, etc., may arise from tissues heterotopically included in the medullary tube at the time of its closure.

DISCUSSION

Dr. George B. Hassin, Chicago: There is and has always been a tendency to classify as syringomyelia a cavity in the spinal cord, regardless of its possible origin. Whether a spinal cavity is the result of so-called gliosis, a dilated central canal, a hemorrhage, a broken-down tumor, a myelitis or focus of softening, it is considered syringomyelia. According to such a view, syringomyelia is not a pathologic entity. Of the foregoing types of cavities, only those due to gliosis should be classified as syringomyelia. In gliosis, the glia is not proliferative and progressive but regressive, that is, there is a breaking up of the glia fibers with ameboid changes in the glia cell bodies. Such a regressive glia causes secondary neural changes. The neural parenchyma also ultimately breaks down and its destruction is associated with secondary mesodermal changes in the form of a membrane lining the cavity and hyperplasia of the blood vessels. The changes mentioned are just the reverse of what has been shown by Dr. Mackay. In his and Dr. Favill's case, the glia was not regressive, but progressive. It appeared as a dense feltwork of thin neuroglial fibers and numerous astrocytes which often were of the giant or monster variety, and the cavity contained no membrane. The impression is that one deals in this case with a gliomatous tumor in the nature of an astrocytoma with an artificial cavity in it. Such cavities have been described as neoplastic syringomyelia, which, in my opinion, should not be classified as syringomyelia, but as pseudo-syringomyelia.

Dr. J. H. Globus, New York: No one has as yet given a satisfactory explanation for the histopathogenesis of syringomyelia.

In the case presented this afternoon, I think a very good case has been made out for the explanation given. It is likely that in this instance some developmental defect was responsible for the formation of cavitation in the cord; and the fact that it was surrounded by a neoplastic process does not exclude the possibility that in this instance the syringomyelia is a form of maldevelopment. Tumors, in a way, are themselves results of malformation, and they may be associated with other forms of malformation, including syringomyelia or syringobulbia. Of course, I think Dr. Mackay is well aware that syringomyelic defects are present in other conditions. One finds them in acquired conditions, such as inflammatory disease of the spinal cord and in arteriosclerosis of the spinal cord. Central gliosis and tumors in which there is no question that the tumor was a primary pathologic condition are often associated with syringomyelia.

This, unquestionably, is a case of an intramedullary neoplasm; I think most likely an ependymoma. But the cavity occurring in it bears all the earmarks of another malformation associated with the tumor, rather than the result of necrobiosis, caused by the new growth.

Dr. Bernard Sachs, New York: As there is a question as to whether there was a true syringomyelia or not, I should like to ask whether the sensory symptoms were not those that one generally accepts as pointing to syringomyelia: were they not present at the beginning of the case? I have not heard any statement concerning that. It is important to be able to determine clinically whether a case is likely to be one of central tumor or syringomyelia, because I think the operative precedure would be largely determined by that. I should like to inquire as to the early sensory manifestations in the case.

Dr. R. P. Mackay. As regards Dr. Hassin's discussion, I am a little bit at a loss to understand what he means when he says a gliosis is not a proliferative condition. One is accustomed to think of gliosis as a form of glial proliferation. I had hoped to point out that the tissue in our case is not a reactive gliosis; it is blastomatous tissue, and in that sense, as Dr. Globus suggested, it is a tumor. However, it is a peculiar and unique type of tumor, and one which we believe it would be better to call a "primary central gliosis." It is a unique tumor in that it always lies in the same place in the cord; that it does not occur anywhere else in the central nervous system; that it does not, although it may last for thirty or forty years, as a rule produce any true tumor in the etymologic sense of the word, that is, a swelling. The cord in this case did not exhibit any increase in size.

A tumor which lasts for nine years as in this case, and never produces any swelling is a unique form of tumor, at least. Therefore, we feel that it should be called a primary central gliosis, to distinguish it from the gliomas on the one hand and from the usual or reactive gliosis on the other hand. For the same reason I cannot agree that it is an astrocytoma, although it is composed for the most part of astrocytes. There are many spongioblasts present in the tissue and yet the growth is much more chronic and fibrillary than are the astrocytomas. In cases in which astrocytoma and syringomyelia have been present together (Kernohan) it has always been possible to distinguish the two histologically.

There were no sensory disturbances in this patient above the first lumbar dermatome. That was the level at which the ependymoglioma occurred. For that reason, Dr. Favill was not able to make a diagnosis of syringomyelia. Consequently one of the lessons to be learned from this case is that syringomyelia may be a "silent" disease. This patient had a cavity in the center of her cord which ran from the first cervical segment to the filum terminale, and had no sensory disturbances except that occasioned by an associated ependymoglioma. Had the dis-

ease in her case been limited to the process in the thoracic cord, she should have had no symptoms at all.

I rather anticipated the criticism that this case does not represent syringomyelia at all. One can only say that the most important authors who have writen on the subject during the past sixty-five or seventy years have described a tissue almost identical with this and have called it syringomyelia. Some of these are Gerlach, Bielschowsky and Unger, Schlesinger, Henneberg, Rosenthal, Jonesco-Sisesti, Bremer and Turnbull. Kernohan goes further and says this tissue is gliotic but not neoplastic. The confusion as regards histology of syringomyelia results from the tendency to degeneration and mesoblastic or collagenous tissue scarring which may eventually mask the original primary central gliosis.

EFFECTS OF ALTERATIONS IN POSTURE ON THE CEREBROSPINAL FLUID PRESSURE

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In a study of the effect of postural alterations on the cerebrospinal fluid pressure, two objections in particular may be made to the attempt to apply observations on animals to human beings: first, the common use in animal experimentation, for example, of ether, an anesthetic which has been definitely demonstrated to disturb the dynamic conditions within the intracranial cavity; second, the difference between the postural habits of man and those of four-footed mammals, which may result in dissimilar pressure reactions when the position of the body is altered as a result of the variations in their respective vascular compensatory mechanisms.

With these objections in mind we have performed on man certain postural experiments, some of which have heretofore been made, and have added some measurements of cerebrospinal fluid pressure in positions which have not been previously utilized, at least in the human subject. The experiments were divided to learn the following facts: (1) the relationship between the cisternal and the lumbar pressure in the sitting position, (2) the effect on the lumbar and on the cisternal pressure of the extraction of spinal fluid, (3) the comparison of the cerebrospinal fluid pressure in the "hands-and-knees" and in the lateral recumbent position, (4) the cisternal pressure in the vertical head-up and in the vertical head-down position and (5) the cisternal pressure in the lateral recumbent and in the supine position.

MATERIAL, TECHNIC AND APPARATUS

The subjects utilized were patients at the Boston State Hospital in whose cases the diagnoses of dementia praecox, dementia paralytica, manic-depressive psychoses, alcoholic psychosis and feeblemindedness had been made. The patients who were selected were in good physical condition and were cooperative. Each experiment was performed in the morning after the patient had rested in bed for approximately one-half hour.

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For the measurement of the lumbar or suboccipital pressure in the lateral recumbent position, the Fremont-Smith or Ayer manometer with a 2 mm. bore was used. Since these manometers measure only pressures above atmospheric pressure, a specially constructed manometer was utilized whenever, because of the position of the patient, the cerebrospinal fluid pressure was expected to be subatmospheric or negative. This apparatus will be described in some detail, since so far as we are aware it has not been previously used in human experimentation.

The manometer[1] (fig. 1) consists of an air pressure control chamber and a U-shaped manometer which is connected by means of stiff rubber tubing to a pipe-stem manometer, stopcock and needle. With the needle in the subarachnoid space, fluid rises in the straight manometer against the air pressure, which is easily adjusted in advance by means of a Luer syringe. If the cerebrospinal fluid pressure is expected to be less than atmospheric pressure, the pressure within the air chamber is lowered beforehand in order to prevent air from being sucked into the

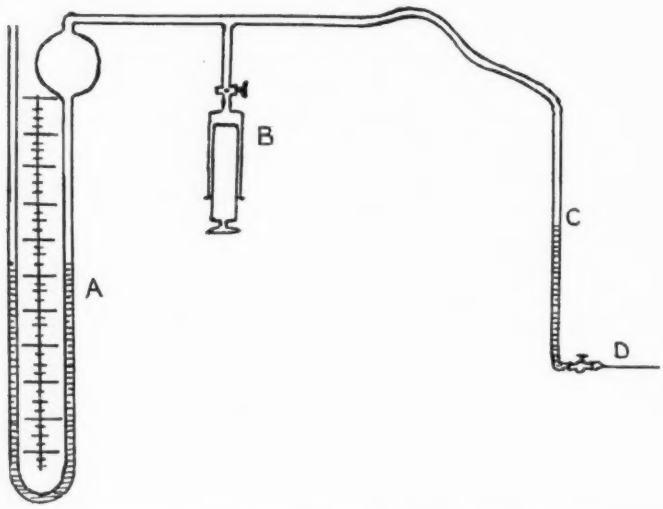

Fig. 1.—Air pressure control manometer. The U-tube (*A*) measures the air pressure. The pressure is controlled by means of a syringe (*B*). *C* is the pipe-stem manometer attached to a needle (*D*).

subarachnoid space. The actual pressure of the cerebrospinal fluid is calculated by taking the difference between the change in pressure in the air chamber and the rise in the pipe-stem manometer. Thus, if the rise in the pipe-stem manometer is 80 mm. and the air pressure within the U-shaped system is diminished by 100 mm. of water, the actual cerebrospinal fluid pressure is —20 mm. of water (that is, 80 —100 mm.). This method furnishes accurate determinations, it may be used for extremely low negative pressures, and it may be controlled so that there is only a slight loss of fluid from the subarachnoid space into the manometer.

In the following experiments the pressure was usually recorded first with the subject in the lateral recumbent position so that the occiput and the spine were in horizontal alinement. For combined cisternal and lumbar readings taken in the

1. The principle of this manometer was suggested to us by Dr. Joseph Slepian, Research Engineer, Westinghouse Electric Company, Pittsburgh.

sitting position the following technic was used: while the subject was in a lateral recumbent position, the lumbar needle was closed, the cisternal needle was connected with the negative pressure system and the air pressure reduced so that when the subject was moved to a sitting position the cisternal reading would be positive and air would not be sucked into the cisterna magna. After this reading was taken, the cisternal needle was closed and the lumbar pressure read. Both needles were never allowed to be open at the same time. Great care was taken that when the subject was in the sitting position the back was straight, the head was neither flexed nor extended, the arms rested on the thighs and the abdominal muscles were relaxed. No readings were recorded until the fluid had reached and maintained its lowest level. A capillary correction of —15 mm. of water was made for each reading. Although a further correction for the loss of fluid from the subarachnoid space into the manometer might be made, this has been ignored since the loss is usually insignificant.

RELATIONSHIP BETWEEN THE SUBOCCIPITAL AND THE LUMBAR PRESSURE IN THE SITTING POSITION

Readings of the lumbar pressure with the subject in the sitting position have been made by many workers, particularly by Barré and Schrapf,[2] Zylberlast-Zand,[3] Ayer[4] and Howe.[5] In animals, Weed[6] has probably made the most detailed study of the effects of changes in posture, with simultaneous suboccipital and lumbar readings made during the rotation of the animal from the horizontal to the head-up and to the head-down position.

Table 1 shows the combined measurements of the lumbar and the cisternal pressure in thirteen subjects in the sitting position. The lumbar pressure ranged from 375 to 565 mm. of water, the average being 467 mm. The cisternal pressure varied from —85 to +45 mm., the average being —7 mm. Noting the distance between the two sites of puncture, namely, the lumbar-cisternal distance, we find a range of from 380 to 530 mm., with an average reading of 484 mm. If the difference between the two pressures is computed, that is, the lumbar minus the cisternal pressure (L minus C), the remainder is seen to be nearly equal to the vertical distance between the two sites of puncture. For example, in case 1, L minus C, or 435 —40 mm., equals 475 mm., which is within 15 mm. of the lumbar-cisternal distance (490 mm.). Again in case 2, with a lumbar pressure of 555 mm.

2. Barré, J. A., and Schrapf, R.: Sur la pression du liquide céphalo-rachidien, Bull. méd., Paris **35**:63, 1921.

3. Zylberlast-Zand, N.: Sur la modification de la pression du liquide céphalo-rachidien sous l'influence du changement de position du corps et de la tête, Rev. neurol. **37**:1217 (Dec.) 1921.

4. Ayer, J. B.: Cerebrospinal Fluid Pressure from the Clinical Point of View in Human Cerebrospinal Fluid, A. Research Nerv. & Ment. Dis., Proc. **4**:159, 1924.

5. Howe, H. S.: Physiological Mechanism for the Maintenance of Intracranial Pressure, in Intracranial Pressure in Health and Disease, A. Research Nerv. & Ment. Dis., Proc. **12**:7, 1924.

6. Weed, L. H.: Experimental Studies in Intracranial Pressure, in Intracranial Pressure in Health and Disease, A. Research Nerv. & Ment. Dis., Proc. **12**:25, 1931.

and a positive cisternal reading of 30 mm., L minus C, or 555 minus 30 mm., equals 525 mm., which is within 5 mm. of the lumbar-cisternal distance (530 mm.). In six of the thirteen cases, the L minus C figure was within 5 mm. of the lumbar-cisternal distance; in four cases, there was a difference of 15 mm.; in three cases, a difference of from 25 to 35 mm. The difference in the latter cases may be ascribed to the imperfections necessarily involved in such postural experiments.

On the basis of the figures for these thirteen cases, a further statement may be made. Since the vertical lumbar-cisternal distance is equal to the difference between the lumbar and the cisternal pressure, from a knowledge of one of these pressures and of the vertical distance between the two sites of puncture one can readily find the other reading by means of the following formula: CP equals LP minus D, or LP equals D plus CP, in which D represents the vertical distance between the lumbar and the cisternal points of puncture; LP, the lumbar pressure, and CP, the cisternal pressure. For example, in case 14, 425 mm. (LP) minus 510 mm. (D) equals —85 mm. (CP) or, vice versa, 510 mm. (D) plus —85 mm. (CP) equals 425 mm. (LP).

As stated before, the range of the thirteen lumbar pressures recorded with the subjects in the sitting position was from 375 to 565 mm., with an average of 467 mm. These figures are much higher than those cited by Barré and Schrapf,[2] who gave from 150 to 400 mm. as the range of pressures in the sitting position. We have never observed as low a pressure as 150 mm. with the subject in the sitting position when the subarachnoid reservoir was intact or when the spinal subarachnoid space was unobstructed.

Zylberlast-Zand [3] gave a still lower maximal figure than Barré and Schrapf, the range in pressure being from 200 to 300 mm., which seems to be correspondingly as low as the pressures she gave for the horizontal position, namely, from 10 to 100 mm. Unfortunately, the workers cited failed to give the detailed technic of their experiments.

Pappenheim [7] remarked that the lumbar pressure with the subject in the sitting position is between 200 and 300 mm. higher than that in the lateral position. Ayer [4] and Fremont-Smith and Kubie [8] stated that the lumbar pressure is approximately doubled when the subject changes from a lateral to a sitting position.

Weed [6] found a comparatively slight change in pressure in rotating laboratory animals from the horizontal to the tail-down position. Evidently, these mammals react to such changes in much less degree than does man. In other words, it appears that in the vertical position, the point along the spine at which zero or atmospheric pressure is found is relatively much nearer the head in man than in these animals. Because

7. Pappenheim, M.: Lumbar Puncture, New York, William Wood & Company, 1925, p. 60.

8. Fremont-Smith, F., and Kubie, L. S.: The Relation of Vascular Hydrostatic Pressure and Osmotic Pressure to the Cerebrospinal Fluid Pressure, in Intracranial Pressure in Health and Disease, A. Research Nerv. & Ment. Dis., Proc. **12**:104, 1931.

of the results that he obtained, Weed stated that only about one third or one quarter of the possible height of the column of fluid in the vertical position is thrown on the dependent part of the nervous system. Such a conclusion, Weed stated, corresponds with the findings of Zylberlast-Zand. The latter author obtained readings of from 200 to 300 mm. in the sitting position, which seem to us to be extremely low, and if they are added to her correspondingly low readings of pressures for the horizontal position of from 10 to 100 mm. would, of course, be lower than the vertical height from the lumbar region to the cisterna magna and would thus check with Weed's results in animals.

Howe,[5] on the other hand, stated, though without giving definite figures, that he found the average horizontal pressure of 150 mm., when added to the average vertical lumbar-cisternal distance of 300,

TABLE 1.—*Combined Lumbar and Cisternal Pressures in the Sitting Position*

Case		Lumbar Pressure, Mm. of Water	Cisternal Pressure, Mm. of Water	Lumbar Minus Cisternal Pressure, Mm. of Water	Vertical Distance Between Puncture Sites, Mm.
1	Dementia praecox	435	—40	475	490
2	Dementia praecox	555	30	525	530
3	Dementia paralytica	375	—30	405	410
4	Dementia praecox	425	—25	450	475
5	Dementia praecox	475	10	465	470
6	Dementia praecox	565	45	520	520
7	Dementia paralytica	400	35	365	380
9	Dementia paralytica	455	—20	475	510
10	Dementia paralytica	435	0	435	450
11	Alcoholic psychosis	485	—30	515	520
12	Alcoholic psychosis	485	10	475	500
13	Dementia praecox	555	10	545	530
14	Dementia praecox	425	—85	510	510
	Average	467	—7	474	484

to be equal to the average lumbar sitting pressure (450 mm.). For the vertical lumbar-cisternal distance in an adult 300 mm. is an extremely low figure; the average figure is nearer 500 mm., with a scattering of readings below and above this.

If in our thirteen cases (table 1) 100 mm. is taken as the average spinal fluid pressure in the horizontal position and is added to the average lumbar-cisternal distance, the result is much higher than the average lumbar cerebrospinal fluid pressure in the sitting position. In table 2 are shown the results of fifteen separate experiments, together with a comparison of the two pressures with the lumbar-cisternal distances. Here again the sum of the lumbar-cisternal distance and the lateral pressure is much higher than the corresponding lumbar pressure in the sitting position. From these figures and those in table 1 it will be noted that there is a much closer relationship between the lumbar sitting pressure and the lumbar-cisternal distance. Thus the average

difference between these two figures in table 1 is only 17 mm. and in table 2, 21 mm. This indicates that the cerebrospinal fluid pressure at the lumbar region, when measured in the sitting position is dependent mainly on the superimposed column of spinal fluid and is essentially unrelated to the pressure in the ordinary horizontal position.

Again, it might be anticipated that the lower the lateral pressure the lower will be the sitting pressure, or vice versa, but it will be seen (table 2) that this is not necessarily true, for in several cases a low lateral pressure was coupled with a high sitting pressure, and vice versa. This, too, points to the probability that the two pressures are expressions of different factors. That such appears to be the case, will be shown later.

TABLE 2.—*Comparison of the Lumbar Pressure in the Lateral and in the Sitting Position with the Lumbar-Cisternal Distance*

Case		Lateral Pressure, Mm. of Water	Sitting Pressure, Mm. of Water	Lumbar-Cisternal Distance, Mm.
1	Dementia praecox	95	435	490
3	Dementia paralytica	165	375	410
5	Dementia praecox	100	475	470
6	Dementia praecox	145	565	520
10	Dementia paralytica	160	435	450
12	Alcoholic psychosis	75	485	500
13	Dementia praecox	160	555	530
14	Dementia praecox	95	425	510
21	Manic-depressive psychosis	145	455	490
22	Dementia praecox	160	475	480
23	Dementia praecox	100	495	520
24	Mental deficiency	60	535	570
25	Dementia praecox	140	460	490
26	Dementia praecox	85	485	525
28	Dementia paralytica	140	515	530
	Average	122	478	499

Comparing now the cisternal pressures in the sitting position, it will be noted (table 1) that in seven of the thirteen cases the pressure was zero or negative and in six it was positive. In the literature we were able to find recorded in reports of human experiments few exact measurements of cisternal pressures. Usually it is stated that this pressure is negative or below zero (Ayer [4]). Grashey,[9] as a result of his studies of the mechanical analogs of the human craniovertebral system, concluded that the pressure at the cisterna-magna is probably zero. Propping,[10] however, found in cadavers that the point of atmospheric pressure was below the cisterna magna, that is, somewhere in the cervical region. Eskuchen [11] found the pressure to be less than atmospheric, in

9. Grashey, H.: Experimentelle Beiträge zur Lehre von der Blut-Circulation in der Schädel-Rückgratshöhle (Festschrift, Prof. Ludwig A. Buchner), Munich, J. F. Lehmann, 1892.

10. Propping: Die Mechanik des Liquor cerebrospinalis und ihre Anwendung auf die Lumbalanästhesie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **19**:441, 1908.

11. Eskuchen, K.: Die Punction der Cisterna cerebello-medullaris, Klin. Wchnschr. **2**:1830 (Oct. 1) 1923.

some cases as low as — 150 mm. of water. There is apparently a rather wide variation in cisternal pressure as there is in lumbar pressure. In our series of thirteen cases (table 1) there is found an average pressure of — 7, which is close to the figure found by Grashey in his experiments.

EFFECT OF THE EXTRACTION OF SPINAL FLUID ON THE CISTERNAL AND THE LUMBAR PRESSURE IN THE SITTING POSITION

Ayala [12] first made use of volume-pressure curves in obtaining a rough estimate of the volume of the cerebrospinal fluid reservoir.

TABLE 3.—*Effect of Drainage on the Lumbar and the Cisternal Pressure in the Sitting Position in Three Typical Cases*

Case		Lumbar Pressure, Mm. of Water	Cisternal Pressure, Mm. of Water	Lumbar Minus Cisternal Pressure, Mm. of Water	Amount Drained, Cc.	Lumbar-Cisternal Distance, Mm.
1	Dementia praecox	435	— 40	475	0	490
		395	— 90	485	10	
		335	—155	490	20	
		275	—225	500	30	
		225	—275	500	40	
		195	—305	500	50	
		135	—350	485	60	
5	Dementia praecox	475	10	465	0	470
		445	— 20	465	10	
		385	— 80	465	20	
		320	—155	455	30	
		285	—175	460	40	
6	Dementia praecox	565	45	520	0	520
		515	— 10	525	10	
		455	— 65	520	20	
		365	—160	525	30	
		315	—205	520	40	
		265	—250	515	50	

Weed and his associates [13] also utilized this relationship in an attempt to estimate the elasticity of the intracraniospinal system.

In this study we are not especially concerned with the volume-pressure factor, but we are interested in comparing the cisteral and the lumbar pressure in the sitting position following successive extractions of fluid.

In seven cases these pressures were simultaneously measured following successive extractions of 10 cc. of spinal fluid by means of a Luer syringe. The total amount of fluid removed ranged in different cases from 30 to 60 cc. As successive amounts of fluid were removed, both pressures, of course, decreased. (During each extraction, or while the pressure at either site was being measured, only one needle

12. Ayala, G.: Die Physiopathologie der Mechanik des Liquor Cerebrospinalis und der rachideal Quotient, Monatschr. f. Psychiat. u. Neurol. **58**:65, 1925.

13. Weed, L. H.; Flexner, L. B., and Clark, J. H.: Effect of Dislocation of the Cerebrospinal Fluid upon Its Pressure, Am. J. Physiol. **100**:246 (April) 1932.

was open.) After each extraction, the difference between the lumbar and the cisternal pressure continued to hold, so that it equaled or nearly equaled the lumbar-cisternal distance [14] (table 3). The pressure at the cisterna magna following extractions of 60 cc. of fluid fell to approximately — 350 mm. of water. In other experiments, not recorded here, in which from 70 to 80 cc. of fluid was removed, the cisternal pressure fell to approximately — 500 mm. Although the fluid was extracted by syringe fairly rapidly, there was no evidence of discomfort to the subject, except perhaps fatigue. None of the patients complained of headache or other cerebral symptoms, though whether or not they had headache was subject to some doubt because of their mental state.

In a consideration of alterations of pressure in the negative direction, we should like to learn whether cerebral symptoms are precipitated by fairly rapid and large extractions of fluid with resulting low intracranial pressure; for we have thought that headache following lumbar puncture might be related to the extent of this factor. There is, of course, a rapid readjustment, as Pappenheim [7] and Solomon [15] have pointed out. The ability of the fluid to maintain a steady state has been stressed by Fremont-Smith and Merritt.[16]

If the leakage of fluid is the important factor in the production of headache following lumbar puncture and if it is apt to occur more rapidly in the upright position, it would be interesting to know the extent of the negative intracranial pressure in the sitting position. This, as our experiments indicate, can be accurately determined only in the sitting position, since the measurement of pressure in the lateral position gives no accurate conception of the pressure in the sitting position.

CEREBROSPINAL FLUID PRESSURE IN THE HANDS-AND-KNEES AND IN THE LATERAL RECUMBENT POSITION

We introduced the hands-and-knees position because here all hydrostatic effects are at a minimum. The prone position might have been used for this purpose if it were not for the complicating factor of abdominal compression.

First, the pressure in the lateral position was noted. The subject was then instructed to assume carefully the prone position and to rise on his hands and knees so that the occiput and spine were in horizontal alinement. The puncture

14. During these experiments, this relationship in some instances did not hold with exactitude. This may be attributed to slight alterations in posture associated with fatigue.

15. Solomon, H. C.: The Effect on Human Cerebrospinal Fluid Pressure of Extraction and Injection of Fluid, with Observations on the Time of Normal Readjustment, in Intracranial Pressure in Health and Disease, A. Research Nerv. & Ment. Dis., Proc. **12**:82, 1931.

16. Fremont-Smith, F., and Merritt, H. H.: Influence of Variations in Fluid Intake on Intracranial Pressure in "Epileptics," Tr. Am. Neurol. A., 1932, p. 499; Arch. Neurol. & Psychiat. **29**:454 (March) 1933.

needle was then, of course, at right angles to the plane of the back and was considered as part of the manometric system in determining the final reading. The length of the needle and the stopcock measured 120 mm., which was added to the height of the fluid in the manometer in determining the corrected reading. In every case in which such readings were made, the level of the cerebrospinal fluid pressure was so low that it was necessary to use the air-controlled system already described.

In fifteen cases it was observed that the pressure in this position was in all but one instance considerably lower than that in the lateral recumbent position. One pressure reading in the hands-and-knees position was as low as —20 and another was —15 mm. The average pressure in the hands-and-knees position in the fifteen cases was 40 mm.,

TABLE 4.—*Comparison of the Lumbar Pressures in Different Positions*

Case	Hands-and-Knees Pressure, Mm. of Water	Lateral Pressure, Mm. of Water	Sitting Pressure, Mm. of Water	Sum of Hands-and-Knees Pressure and Lumbar-Cisternal Distance, Mm.
12 Alcoholic psychosis	—20	75	485	480
13 Dementia praecox	95	160	555	625
14 Dementia praecox	15	95	425	440
21 Manic-depressive psychosis	30	145	455	520
22 Dementia praecox	45	160	475	520
23 Dementia praecox	10	100	495	505
24 Dementia praecox	20	140	460	580
26 Dementia praecox	20	105	485	480
28 Dementia paralytica	75	140	515	505
29 Dementia praecox	85	105	...	...
40 Dementia praecox	—15	90	...	...
41 Dementia praecox	20	120	475	...
42 Dementia praecox	105	185	...	...
43 Dementia paralytica	75	160	...	...
44 Dementia praecox	30	75	475	525
Average	40	124	464	518

while that in the lateral position was 124 mm. of water (table 4). In several instances the cisterna magna was punctured and the pressure was read simultaneously with the lumbar pressure. In the hands-and knees position these two pressures were identical.

CISTERNAL PRESSURE IN THE VERTICAL HEAD-UP, VERTICAL HEAD-DOWN, SUPINE AND LATERAL POSITIONS

In this series of experiments the subject was placed on a tipping table constructed so that the subject could be tilted to the vertical head-up, the vertical head-down or the ordinary lateral position. The body was held in place by means of a canvas harness which encircled the shoulders, chest and abdomen and was buckled to the sides of the table. For further stabilization a strap was placed around the subject's legs, and his feet were allowed to rest against braces to which they were secured. The subject lay on his back, so that his head, covered with a leather helmet, was clear of the end of the table and rested on a cross-bar. Strappings from the head-gear to the side pieces of the table held the head securely in

place. All strapping was applied so that there was a minimum of compression of the chest and the abdomen. A comparison of the pressure readings in the supine position with the strapping on and off was always made and showed insignificant differences.

In order to puncture the cisterna magna with the strapping applied, the top of the table was rotated sidewise, so that the subject was in the lateral position. Following the puncture, the subject was returned to the supine position. The needle was connected with a right-angled manometer having a 2 mm. bore and the pressure measured.[17] The negative pressure system was then connected, the air pressure adjusted, the subject rotated to the head-up position and the pressure read. The subject was then brought back to the supine position, and another reading was taken; he was then rotated to the vertical head-down position and the pressure was determined. A final reading in the supine position was then made. The straps and the head-gear were removed, the subject was placed in the lateral recumbent position, and the pressure was measured. For purposes of comparison with the vertical head-up position, a reading was usually taken in the sitting position.

TABLE 5.—*Cisternal Pressure, Showing the Variations with Postural Change*

Case		Supine Pressure, Mm. of Water	Vertical Head-Up Pressure, Mm. of Water	Vertical Head-Down Pressure, Mm. of Water	Lateral Pressure, Mm. of Water	Sitting Pressure, Mm. of Water
58	Dementia praecox	160	−10	495	...	....
59	Dementia paralytica	140	20	515	...	....
62	Dementia praecox	150	−40	550	135	−25
65	Dementia praecox	145	5	545	140	30
66	Dementia praecox	120	−15	555	55	−55
67	Dementia praecox	120	−45	550	75	−45
69	Dementia praecox	145	25	435	120	10
70	Dementia praecox	120	−15	425	75	−50
	Average	137	− 9	509	100	− 22

This technic was carried out on eight subjects (table 5). When the subject was brought back to the supine from the head-up position, the pressure assumed sometimes a slightly higher and at other times a slightly lower level than that of the original reading. Following the head-down determination, the supine pressure returned to a reading slightly lower than the original reading in that position and then resumed its initial level. The vertical head-up pressure in the cisterna magna ranged from −45 to +25 mm. The average fall in pressure between the supine and the vertical head-up position was approximately 146 mm. (from 137 to −9 mm.). In marked contrast to this reaction, the average rise in pressure that occurred when the body was rotated from the supine to the vertical head-down position was 372 mm. (from 137 to 509 mm.).

17. In order to obtain the corrected pressure, the length of the needle and the stopcock is deducted from the reading in the manometer.

Although every means was taken to encourage bodily relaxation, the nature of such postural experiments makes complete passivity of the subject difficult. To check this factor, the readings in the sitting position were usually compared with those in the vertical head-up position. (With complete relaxation these two pressures should be practically equal.) In six such comparisons, the head-up pressure was slightly lower than the sitting pressure in three cases; in two cases the latter was lower than the former; and in one case they were equal. In order to ascertain the state of bodily passivity in the head-down position, the cisternal pressure in this position was compared in two subjects before and during narcosis produced by amytal. In both instances the pressure before narcosis was only 35 mm. higher than that during narcosis.

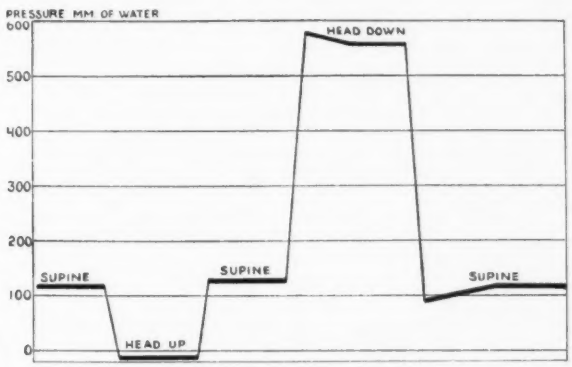

Fig. 2 (case 66).—Diagram showing the effect on the cisternal pressure of tilting the subject from the supine to the vertical head-up and the vertical head-down position. Note that the change in pressure from the supine to the head-down position is approximately three times as great as in the opposite postural shift.

Thus, the vertical pressures recorded in table 5, although in some cases quantitatively not exact, are sufficiently accurate to indicate the marked difference between the change in pressure which occurs when the subject is tipped from the supine position to the vertical head-up and head-down positions.

CISTERNAL PRESSURE IN THE LATERAL RECUMBENT AND IN THE SUPINE POSITION

In twelve experiments the cerebrospinal fluid pressure in the lateral recumbent and in the supine position were compared. The tipping table was used, but no strapping or head-gear was applied to the body. The cisterna magna was punctured with the subject in the lateral position and the pressure measured. The subject was then carefully placed in

the supine position and the pressure determined. Table 6 shows the readings obtained, including those for six subjects from the foregoing study (table 5). In fourteen of the eighteen comparisons the pressure in the supine position was higher than that in the lateral position; in two instances the reverse was true; and in two other cases the pressures were equal. The average pressure in the lateral recumbent position was 100 mm. and in the supine position, 126 mm. Similar results were obtained by Lewis and Ravdin [18] who experimented with dogs narcotized with amytal.

TABLE 6.—*Cisternal Pressures in the Lateral and in the Supine Position*

Case		Lateral Pressure, Mm. of Water	Supine Pressure, Mm. of Water
75	Dementia praecox	125	115
76	Dementia praecox	115	135
77	Dementia paralytica	75	125
78	Dementia praecox	85	85
79	Manic-depressive psychosis	65	100
80	Dementia praecox	75	105
81	Dementia praecox	140	105
82	Dementia praecox	55	125
83	Dementia praecox	110	110
84	Dementia praecox	125	150
85	Dementia praecox	115	160
86	Dementia praecox	120	160
62	Dementia praecox	135	150
65	Dementia praecox	140	145
66	Dementia praecox	55	120
67	Dementia praecox	75	120
69	Dementia praecox	120	145
70	Dementia praecox	75	120
	Average	100	126

COMMENT

Any consideration of the factors which influence the cerebrospinal fluid pressure must take into account the fact that this fluid is contained in a space which has four walls: (1) the dura, (2) the arteries, (3) the capillaries and (4) the veins. The dural wall, because of its make-up and attachments, may well be spoken of as rigid or practically so. The arteries, pumped up to an internal pressure of from 60 to 100 mm. of mercury, also form a relatively rigid wall. The capillaries form a wall of less rigidity, and the veins form a wall which is exceedingly elastic (fig. 3).

Changes in the arterial pressure do not, under ordinary physiologic conditions, affect the cerebrospinal fluid pressure, because the slight

18. Lewis, R. M., and Ravdin, I. S.: Cerebrospinal Fluid Pressure During Alterations in Posture, Arch. Neurol. & Psychiat. **24**:1291 (Dec.) 1930.

bulging of the arterial wall which occurs with a rise in the arterial pressure is readily compensated for by a collapse of the venous wall. The arterial pressure is then fully supported by the arterial wall and the change in pressure is not transmitted to the cerebrospinal fluid pressure. These same factors operate to prevent a decrease in the arterial pressure from being transmitted to the cerebrospinal fluid. Moreover, the capillary pressure does not influence the cerebrospinal fluid pressure except as it changes the balance between production and absorption of the fluid; simple changes in the volume of the capillary bed are readily compensated for by changes in the volume of the venous bed. Any increase in venous pressure causes a bulging of the venous wall. Neither the capillary (arterial), arterial nor the dural wall moves sufficiently to make the venous wall support the venous pressure. The change in venous pressure is therefore transmitted directly to the cerebrospinal fluid.

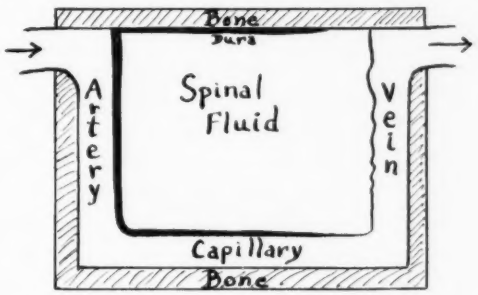

Fig. 3.—Schematic diagram showing the "four walls" (dura, arteries, capillaries and veins) which enclose the cerebrospinal fluid. The dura is the least elastic and the veins the most elastic wall.

Definite experimental evidence has been adduced with regard to the effect of changes in the arterial and in the venous pressure on the cerebrospinal fluid pressure. It has been shown that before changes in the cerebrospinal fluid pressure occur as a result of arterial influences, it is necessary that the arterial pressure undergo wide and rapid variations.[19] Furthermore, the work of Fremont-Smith and Merritt [20] indicated that a continued high arterial pressure has no effect on the cerebrospinal fluid pressure. In contrast to this arterial reaction, alterations in the venous pressure produce ready and marked changes in the cerebro-

19. Becht, F. C.: Studies on the Cerebrospinal Fluid, Am. J. Physiol. **51**:1 (Feb.) 1920. Weed.[6]

20. Fremont-Smith, F., and Merritt, H. H.: Relationship of Arterial Blood Pressure to Cerebrospinal Fluid Pressure in Man, Arch. Neurol. & Psychiat. **30**:1309 (Dec.) 1933.

spinal fluid pressure (Hill,[21] Becht,[19] Weed and Hughson,[22] Myerson and Loman,[23] and others).

During postural alterations, changes in the arterial pressure are not sufficiently marked to influence the cerebrospinal fluid pressure. The carotid pressure, for example, undergoes a change of approximately 30 mm. of mercury when the body is tilted from the horizontal to the vertical position. Furthermore, it usually partially returns to its original level while the vertical position is being maintained.[23] On the other hand, the internal jugular pressure during the same maneuver not only reacts conspicuously to the force of gravity, but once it reaches its new level it remains unchanged.

It is known that the cerebrospinal fluid pressure is normally only a few millimeters of water above the pressure in the veins where they leave the skull and the spine. It is possible, however, for the cerebrospinal fluid pressure to be elevated well above the pressure in these veins, and when this occurs it is evidence that there is interference with the cerebral and spinal venous drainage. This might be produced, for example, by a tumor compressing one or both lateral sinuses or by an increase in the volume of the cerebrospinal fluid, which would act like a tumor by compressing the veins and interfering with their drainage. Normally, however, such an increase in the volume of the cerebrospinal fluid is rapidly taken care of by a readjustment of the production-absorption mechanism; witness the rapid return of the cerebrospinal fluid pressure to normal after 10 cc. of a physiologic solution of sodium chloride has been injected into the lumbar sac. Thus, if the cerebrospinal fluid pressure is elevated well above the venous pressure and the interference with venous drainage is being produced by the increased volume of the cerebrospinal fluid, this is absolute evidence of a derangement of the normal production-absorption mechanism. Any condition in which there is a blockage to intracranial and intraspinal venous drainage is pathologic and not of concern in the present study except that we must note that it constitutes a special case which is no exception to the general rule that the cerebrospinal fluid pressure is a reflection of the intracranial and intraspinal venous pressure.

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21. Hill, L.: Physiology and Pathology of the Cerebral Circulation, London, J. & A. Churchill, 1896.

22. Weed, L. H., and Hughson, W.: Intracranial Venous Pressure and Cerebrospinal Fluid Pressure as Affected by the Intravenous Injection of Solutions of Various Concentrations, Am. J. Physiol. **45**:3 and 531, 1919.

23. Myerson, A., and Loman, J.: Internal Jugular Venous Pressure in Man: Its Relationship to Cerebrospinal Fluid and Carotid Arterial Pressures, Arch. Neurol. & Psychiat. **27**:836 (April) 1932. Loman, J., and Myerson, A.: The Action of Certain Drugs on the Cerebrospinal Fluid and on the Internal Jugular Venous and Systemic Arterial Pressures of Man, ibid. **27**:1226 (May) 1932.

Spinal and cranial venous pressure are influenced by:

1. The position of the right side of the heart with respect to the neural axis (fig. 4). If the position of the body is such that the heart, which is the true venous outlet, lies above the brain and the spinal cord, the venous pressure is high. If, on the other hand, the heart lies below the cerebrospinal axis the venous pressure is low.

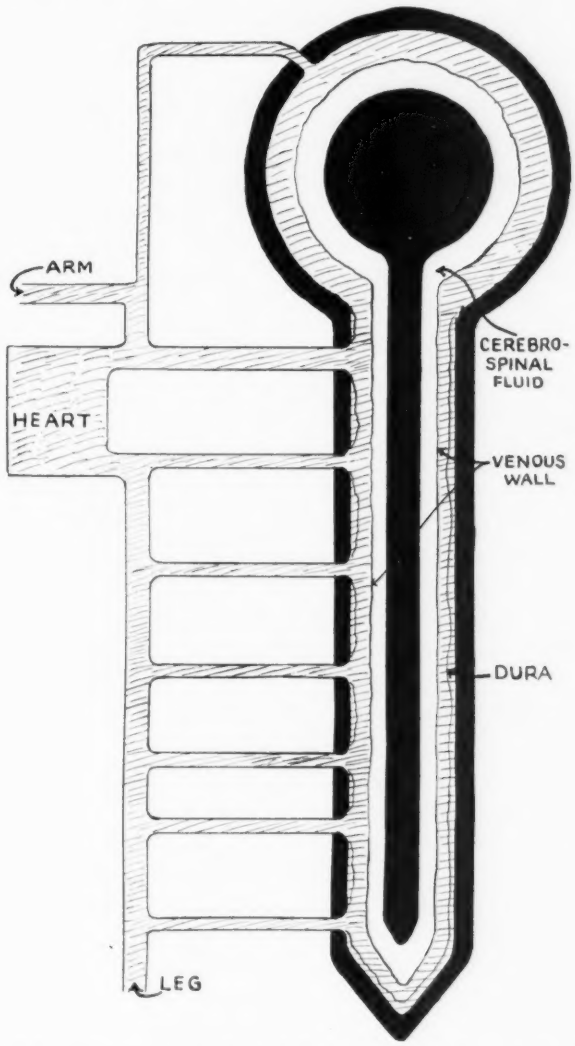

Fig. 4.—Schematic representation of the intracraniospinal cavity in relation to the venous system. The solid black areas represent the brain, cord and bone. The arteries have been omitted, since they do not seem to have any significant elastic effect.

2. The volume of the blood in the great veins. The general venous pressure depends on the degree to which the veins are distended by the blood which they contain. Anything which tends to increase the volume of blood in the abdominal and in the thoracic veins tends to increase the pressure in their immediate tributaries. If the arms, legs or viscera are below the great veins, blood tends to accumulate in these dependent parts and the venous pressure in the great veins is decreased. If, on the other hand, the arms, legs or abdomen are above the great veins, blood tends to drain out of them and to accumulate in the great veins and so increases the pressure.

3. The weight of the viscera lying on the great veins, the channels of the cerebral and the spinal venous drainage. The intestinal tract, the liver, etc., lying against the great veins, tend to compress them, to impede the flow of blood and to raise the venous pressure.

TABLE 7.—*Cisternal and Internal Jugular Pressures in the Lateral Recumbent, "Quadruped" and Sitting Positions*

	Case 35 Dementia Praecox		Case 39 Dementia Praecox		Case 44 Dementia Praecox		Case 45 Dementia Praecox		Case 48 Dementia Praecox	
Position	C*	J*	C	J	C	J	C	J	C	J
Lateral recumbent	120	105	145	65	75	60	175	90	145	80
"Quadruped"	—50	15	60	10	30	—20	50	55	—5	50
Sitting	0	10	5	..	—25	—45	35	30	10	40

* C indicates the cisternal pressure, and J, the internal jugular pressure, in millimeters of a 2 per cent solution of sodium citrate.

4. The tension of the thoracic and the abdominal muscles. Expiratory effort causes an increase in the venous pressure, and inspiration, a decrease. Changes in the intra-abdominal pressure due to contraction or relaxation of the abdominal wall are reflected in changes in the venous pressure. Thus, in the hands-and-knees position, the cerebrospinal fluid pressure is extremely low, for all of the factors listed as influencing the venous pressure are operating to lower it. The combined measurement of the internal jugular and the cisternal pressures in the lateral recumbent and in the hands-and-knees position shows that these pressures vary in the same direction and approximately to the same degree. Similarly, in the vertical position these two pressures undergo similar and comparable changes (table 7). Again, under such conditions as jugular compression, they both rise to approximately the same degree. If, however, the cerebrospinal fluid pressure is increased, the internal jugular pressure remains unaffected and the cerebrospinal fluid pressure rapidly returns to approximately the level of the jugular pressure. It appears, therefore, that the venous pressure stands in a causal relationship to the cerebrospinal fluid pressure. The changes in the

cerebrospinal fluid pressure that have been noted in the vertical position are such that they may be interpreted as due to changes in the height of the column of spinal fluid, but at times such an explanation does not apply. On the other hand, the hypothesis that the cerebrospinal fluid pressure is a reflection, in the main, of the venous pressure appears to be borne out by the foregoing data.

SUMMARY AND CONCLUSIONS

Observations of the cerebrospinal fluid pressure were made in the following positions: sitting, lateral recumbent, vertical (head-up and head-down), "quadruped" (hands-and-knees) and supine.

The following observations and conclusions are made:

1. The cerebrospinal fluid pressure measured at the lumbar region when the subject is sitting is closely related to the vertical lumbar-cisternal distance. The cisternal pressure in this position was negative in seven cases and slightly positive in six cases.

2. The lumbar minus the cisternal pressure is equal or nearly equal to the vertical lumbar-cisternal distance. Thus, from a knowledge of two of these factors, an approximation of the third can be obtained.

3. The lumbar pressure in the sitting position cannot be correlated with the corresponding pressure in the lateral recumbent position, for the pressure in the latter position may be low and that in the former may be relatively high, or vice versa.

4. The pressure in the "quadruped" position was in every case much lower than the corresponding pressure in the lateral recumbent position.

5. The increase in the cisternal pressure when the subject was tilted from the horizontal to the vertical head-down position was approximately three times as great as the decrease in the cisternal pressure when the subject was tilted from the horizontal to the vertical head-up position.

6. The supine pressure is usually slightly higher than the corresponding lateral recumbent pressure.

The observations made on the cerebrospinal fluid pressure indicate that although the pressure receives its initial force from the capillaries of the choroid plexus it is modified by a constantly shifting set of factors, the essential one being the venous pressure. In view of the extremely elastic venous wall which separates the cerebrospinal fluid from the thoracic, abdominal and external pressures it seems inappropriate to refer to the intracraniovertebral cavity as a closed box or semi-rigid container.

MICROCEPHALIA VERA

A STUDY OF TWO BRAINS ILLUSTRATING THE AGYRIC FORM AND THE COMPLEX MICROGYRIC FORM

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Microcephalia vera, as a pathologic entity, has become better understood during the past few decades owing to the cooperation of the clinicians, the embryologists and the pathologists. The clinicians have added to the literature on the subject many instructive case reports which have thrown enlightenment on the physical aspects, anthropometric measurements, neurologic and psychiatric deviations, etc., all of which have increased knowledge of the results of defective development of the brain during intra-uterine life. From the pathologic studies of the condition one can determine the relationship between the pathologic picture disclosed in the central nervous system and comparable embryologic facts relating to teratologic formations during the embryonic development of the cerebral hemispheres. Furthermore, one wishes to inquire into the process of formation of the so-called heterotopias and the anomalies of the cerebral cortex during its earliest elaboration.

HISTORICAL REVIEW AND THEORIES OF MICROCEPHALY

Microcephaly is defined as "a condition or characteristic presented by a small or imperfectly developed head." This is a purely descriptive definition and lacks the elaboration or accuracy of modern standards. Today the definition of microcephaly presupposes three conditions: (1) a reduction of the volume of the brain, especially of the cerebral hemispheres; (2) a smallness and abnormal form of the cranium; (3) anomalies of the form and constitution of the brain, which can be variable in one part and normal in others.

It is of interest to review historically the development of theories of the genesis of microcephalia vera. Castile, quoted by Whitney,[1] stated that in certain tribes of Central Asia microcephaly was so com-

From the Pathological Laboratory of the National Hospital for Diseases of the Nervous System, Queen Square, London.

Read by title at the Sixtieth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 6, 1934.

1. Whitney, E. A.: M. J. & Rec. **130**:158, 1929.

mon that the natives looked on it as natural. According to Whitney,[2] microcephaly was common among native bushmen of Australia; in the earliest writings, sculpture and drawings one finds perfect descriptions of microcephaly. "Certain skulls and portraits found in Central America lead one to believe that microcephaly was fairly common among those early and forgotten races."

Tredgold [3] laid stress on the cranial shape and expressed the belief that this feature is as important as the measurements of the skull. He stated that "true microcephalics have not only a reduction of cranial measurements, but visible and palpable loss of normal rounded contours."

Schaffer [4] evolved a purely mechanical theory of microcephaly, viz., "an insufficient development of the wings of the sphenoid bone which created an obstacle to the development of the sylvian fissure, of the island of Reil, of the central convolution and of the frontal lobes."

Klebs [5] thought it possible that microcephaly was an atrophy due to compression exercised by infrequent contractions of the uterus. Gerhardt [6] attributed it to a compression by retroflexion of the gravid uterus; Falkenheim,[7] to a mechanical effect of other uterine traumatisms. Sapolini,[8] Bischoff,[9] Klebs,[5] Jensen [10] and others claimed as a cause of microcephaly an abnormal straightness of the carotids, the carotid canals thus producing a deficient cerebral circulation. Carl Vogt [11] considered microcephaly as a form of atavism. This conception, long since abandoned, was shared by Giacomini in regard to his true microcephaly, type B.

Brushfield and Wyatt [12] hypothesized that "the anomaly may be due to a reversionary factor or also to the production by vascular occlusion and other factors of tissue defects in the foetal brain." Mingazzini, according to Brunschweiler,[13] thought "that in certain specific pathological conditions, old phylogenetic forms can again become manifest,

2. Whitney, E. A.: M. J. & Rec. **135**:166, 1932.

3. Tredgold, A. F.: Mental Deficiency, ed. 5, London, Ballière, Tindall & Cox, 1929.

4. Schaffer, quoted by Brunschweiler.[13]

5. Klebs: Berl. klin. Wchnschr. **10**:454, 1873.

6. Gerhardt, cited by Brunschweiler.[13]

7. Falkenheim: Berl. klin. Wchnschr. **19**:284, 1894.

8. Sapolini: Ann. univ. di med., Milano **123**:369, 1870.

9. Bischoff: Sitzungsb. d. math.-phys. Cl. d. k. bayer, Akad. d. Wissensch. zu München **2**:163, 1872.

10. Jensen, J.: Arch. f. Psychiat. **14**:752, 1883.

11. Vogt, Carl: Arch. f. Anthropol. **2**:129, 1867.

12. Brushfield and Wyatt: Brit. J. Child. Dis. **23**:265, 1927.

13. Brunschweiler, H.: Schweiz. Arch. f. Neurol. u. Psychiat. **21**:246, 1927; **22**:73 and 269, 1928.

since modifications of perfectioning, which produce young phylogenetic forms, have not been able to effectuate themselves."

These and many more or less mechanical and atavistic theories have been advanced to explain microcephaly, but within the past few decades attention has been directed more and more to embryologic and developmental defects, as the following survey discloses.

Giacomini [14] classified microcephaly into three types: (1) pseudomicrocephaly, in which the reduction of the brain substance is due to direct pathologic processes such as porencephaly, atrophy, hydrocephaly, etc.; (2) true microcephaly, which represents a purely infantile brain, in spite of individual variations, and, (3) a combined microcephaly, which includes cases due to pathologic processes of a general order.

Aeby [15] and Gratiolet [16] opined that microcephalia vera is caused by cerebral anomalies due to endogenous pathologic factors, especially to pathologic conditions of the embryonic tissue. Virchow at first thought that primary microcephaly was due to exogenous factors, such as mechanical causes, including the consequences of extracerebral anatomic circumstances, "or the possibility of something exercising a compression on the brain during its evolution." He later discarded this theory in favor of that of a pathologic process in the brain, but he did not state its mechanism, its seat or its origin. He admitted that leptomeningitis, with a succeeding hydrocephalus, could be an internal cause of this anomaly.

It is in the work of von Monakow's [17] school that the modern and prevailing theories of microcephalia vera had their inception. These workers believed that the anomaly originated chiefly in the embryonic period and that the pathologic factors acted on a tissue in the early stage of development. They established the idea that "these cerebral malformations mark an arrest of development, and more especially and in principle, produce a fixation at the precise point of embryonic evolution. The malformations will be, therefore, in some way the crystallization of a phase, which in normal evolution would have been only transient." They also ventured the opinion that certain heterotopias were caused by the effort of the embryonic tissue after an arrest, or slowing, to reestablish itself and to make up in some way for the time lost.

The origin of some anomalies of cerebral formation, of which microcephalia vera is a major one, can be accounted for by a disease of the fetal substance, or of the germ cell itself, dating from before conception. Thus the anomaly depends almost entirely on the precise time at which

14. Giacomini, cited by Brunschweiler.[13]

15. Aeby: Arch. f. Anthrop. **6**:263, 1873-1874; **7**:1, 1874.

16. Gratiolet, P.: Mém. Soc. d'antrop. de Paris **1**:61, 1860-1863.

17. von Monakow, C.: Schweiz. Arch. f. Neurol. u. Psychiat. **18**:3, 1926.

the teratologic influence appears. Porter and Carter [18] considered that microcephalia vera is the result of an arrest of cerebral development at the fifth month of intra-uterine life and that the small skull is merely molded to the brain. Mall [19] believed that these malformations were not due to general and hereditary causes but were produced by changes in environment, i. e., faulty implantation, probably affecting the development of the normal ovum. Marcus [20] and Murphy [21] expressed the opinion that microcephaly is the outcome of pronounced neuropathic stock. From the records of the Elwyn Training School [2] (referred to by Whitney [1]) seven cases of microcephaly in one family and in twins are reported.

Goldstein [22] stated that the central nervous system is readily affected by external factors. Child [23] contended that the region of greatest activity, i. e., the region of the head, is most easily inhibited by external agents and that microcephaly is a characteristic result of differentiated inhibition along the polar axis. Whitney [1] raised the question whether microcephaly can be one step in the evolution of the configuration of the human head as it exists, the most important factor of which is the arrest of development occurring about the fourth or fifth month of gestation, with the cause generally unknown.

Buzzard and Greenfield [24] suggested that many cases of microcephalia vera may be the result of slight degrees of atrophic sclerosis affecting the hemispheres. Hereditary factors explaining microcephaly were discussed by Filhom,[25] who reported a case of microcephaly in which the parents were cousins and three brothers were microcephalic. Both parents had had syphilis and were alcoholic. Watanabe [26] reported a case of microcephaly in which the parents were cousins; the patient had four brothers; the one preceding the patient was microcephalic. Marcus' [20] patient with microcephaly was a third child, whose parents were first cousins.

Whitney [2] recorded four cases of microcephalic twins, three pairs of the same sex and one of dissimilar twins. He also found records of

18. Porter, L., and Carter, W. E.: Management of the Sick Infant, St. Louis, C. V. Mosby Company, 1924, p. 324.

19. Mall, F.: J. Morphol. **19**:1, 1908.

20. Marcus, J. H.: Arch. Pediat. **42**:593, 1925.

21. Murphy, D. P.: Surg., Gynec. & Obst. **47**:201, 1928.

22. Goldstein, L.: Radiogenic Microcephaly: A Survey of Nineteen Recorded Cases, with Special Reference to Ophthalmic Defects, Arch. Neurol. & Psychiat. **24**:102 (July) 1930.

23. Child, C. M.: General Relationship Between Susceptibility and Physiologic Condition, Arch. Int. Med. **32**:647 (Nov.) 1923.

24. Buzzard, E. F., and Greenfield, J. D.: Pathology of the Nervous System, London, Constable & Co., Ltd., 1921.

25. Filhom: Pediatria **32**: 185, 1924.

26. Watanabe, quoted by Marcus.[20]

from one to seven cases of microcephaly in one family. Brushfield and Wyatt,[12] Tredgold,[3] Whitney[2] and others recorded familial tendencies in microcephaly.

Brunschweiler's[13] review of microcephalia vera is the most extensive study of this subject to date. He considered that primordial pathogenic factors, such as toxins, alcoholism, syphilis, and nutritional toxemia, acting on the embryo itself or on the already altered germinal cells before conception, are frequent causes of microcephaly. He also admitted that factors which can transmit a hereditary taint are potent in its causation. This may explain the cause of microcephaly in twins. He believed that arrest of development can exist without any pathologic process of a general nature, such as meningitis, encephalitis, macular alterations, etc. In other words, "it is necessary, in every case of microcephalia vera, to distinguish, if possible, which are pure examples of essential disturbances of development, and those in which an arrest of development is only secondary to anatomic pathologic processes of a general order."

In this connection, one of us (J. M. W.) ventures to propose as a possible cause of microcephaly the extensive use of certain contraceptives. This was suggested by the observation of a fairly large group of microcephalic children with normal siblings, with one or both parents of the upper intellectual strata and with no ascertainable hereditary stigmas. In five of these cases, pregnancy had not been desired, and such contraceptives as compound solution of cresol, corrosive mercuric chloride and even plain water had been used. Is it not possible that at least one spermatozoan was not injured sufficiently to prevent its fertilizing the ovum but was sufficiently damaged that, after fertilization had taken place, the parts of the developing central nervous system phylogenetically most recently acquired, viz., the cerebral cortex, ceased to elaborate normally at about the fourth or fifth month of embryonic development?

Recently there has been creeping into the literature on microcephaly both experimental and clinical evidence of an arrest of development produced in the germ, or fetus, by means of irradiation of the female pelvis just previous to, or in the early months of, pregnancy.

Försterling[27] irradiated rabbits with roentgen rays and produced retardation of growth of the skull in addition to ocular defects. Goldstein and Murphy[28] reported a case of postconception irradiation with microcephaly. Petenyi, referred to by Murphy,[21] reported on sixteen of thirty-eight children born of mothers fifteen of whom had been irradiated in early pregnancy; these children showed a disturbance of

27. Försterling, Karl: Zentralbl. f. Chir. **33**:521, 1906.

28. Goldstein and Murphy: Am. J. Obst. & Gynec. **18**:189, 1929.

health or development and gross anatomic defects. Goldstein and Murphy emphasized the possibility that postconception irradiation of the pelvis produces cerebral arrest in the development of the embryo.

Murphy [21] concluded that cerebral defects experimentally produced in the new-born may be compared with an arrest of cerebral development following irradiation of the intra-uterine fetus.

Brunner and Schwarz [29] irradiated the heads of young dogs four days after birth and found that fourteen days later the dogs were backward in growth and had epileptiform convulsions. Microscopically there was a high grade of cellular swelling of the brain cells. Krukenberg [30] irradiated two dogs with the roentgen rays, one in the fore part and the other in the hind part of the body. The first animal developed poorly in the subsequent two months, being unable to walk or feed itself. Its head remained smaller than normal, and cerebral defects with ataxia, tremor and visual disturbances were found. The second dog developed normally.

Doll and Murphy [31] reported that twenty-five of seventy-five children irradiated in utero were defective at birth. Fifteen of these twenty-five were feebleminded and of the microcephalic type. Doll and Murphy concluded that irradiation during pregnancy is one preventable cause of mental deficiency and of microcephaly in particular.

Goldstein [22] concluded, after his review of nineteen cases of microcephaly in children with ocular defects, that irradiation acts somewhat similarly to toxic factors or environment in arresting fetal development. Zappert [32] stated that irradiation of the uterus in the early months of gestation causes microcephaly with mental defects in 50 per cent of instances.

It is important to recall that the development of the central nervous system begins in the second week of embryonic life, and the rapidly dividing and differentiating cells of the central nervous system are most sensitive to inhibitory influences at that time. This fact explains the causes for the fifteen of the nineteen cases of microcephaly already mentioned in which irradiation had been used in the first month or two of pregnancy, and it further stresses the susceptibility of the embryonal nerve cells to irradiation, a fact which should be considered by all physicians who are contemplating the irradiation of the female pelvis for any cause.

Considerable experimental and clinical evidence is available that the irradiation of the female pelvis just before or during the first months

29. Brunner and Schwarz: Wien. klin. Wchnschr. **21**:587, 1918.

30. Krukenberg: Verhandl. d. deutsch. Röntgen. Gesellsch. **5**:70, 1909.

31. Doll and Murphy: Am. J. Psychiat. **9**:871, 1929.

32. Zappert, J.: Wien. med. Wchnschr. **75**:1118, 1925.

of pregnancy is not an infrequent cause of microcephaly. Further light from such studies and statistics should be adduced. It is also important that no opportunity be lost to study the brains of microcephalic idiots whose mothers are known to have been irradiated at a definite period of gestation.

PATHOLOGIC STUDIES

All recent work on the pathogenesis of microcephalia vera bears out the conclusions of von Monakow, who in 1921 opined that the pathogenesis of microcephaly lies in two groups of factors: (1) toxic, including alcohol, syphilis and metabolic toxins acting either on the embryo itself or affecting the germ cells prior to conception, and (2) general pathologic processes, such as meningitis or encephalitis, in the fetus.

It can thus be concluded that no single factor or theory is sufficient to account for microcephaly and for the wide variation of anomalies in the many brains studied, as one encounters evidences not only of inherent want of development but also of antenatal disease and degeneration. Practically all the brains studied in this category showed an arrest of cerebral development corresponding to about the fourth or fifth month of fetal life.

For example, Brushfield and Wyatt's [12] patients presented as a most striking feature "small, shrunken and misshapen convolutions, and generalized hypoplasia causing more or less complete lack of normal convolutional appearance." Twenty per cent of the patients showed hydrocephaly, porencephaly, etc. Sixty per cent presented internal hydrocephalus; in one third the dilatation was limited to the lateral and third ventricles; the cortex was ⅛ inch (0.32 cm.) thick.

Microscopically the cerebral cortex showed definite paucity of neurons; the precentral gyrus was almost devoid of healthy pyramidal cells. There was relative integrity of the cerebellum.

Freeman [33] reported four cases of microcephaly with diffuse gliosis. The cortex and basal ganglia showed evidence of defective development from a cytologic and architectural point of view. Much fat was seen scattered dustlike throughout the gray matter, inside and outside the cells and in the compound granular cells about the vessel walls.

Brunschweiler compared the microscopic observations in his cases of microcephalia vera with observations on normal brains of the same age and concluded: "By comparison with normal sections, the hemispheric wall from an architectural point of view represents a fixation at a definite embryonic phase, the internal construction of the hemisphere comparing exactly in his cases to that of a four months fetal brain."

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33. Freeman, W.: Brain **50**:188, 1927.

Sachs [34] said: "The brain in these cases is primarily responsible for the early closure of the cranial sutures, and there is a microgyria present with agenesis of the cortex."

HETEROTOPIAS

Heterotopias are formations of gray matter resting in places where normally gray matter does not occur. Histologically one finds in microcephalic brains a considerable development of a very primitive interstitial substance in the deeper part of the cortex, which appears to be identical with that of certain very primitive heterotopias and with that of the hemispheric wall of the fourth embryonic month.

To quote further from Brunschweiler's report: "Some nervous functions cease to evolute, others continue, none in a fantastic way, but follow an ordered plan as if nature safeguarded first of all the organs not immediately necessary to life, e.g., the cerebral trunk, so astonishingly well developed in comparison to the cerebral hemispheres which remain primitive."

"The olive, as an organ of greatest differentiation of the cerebral trunk, is the most poorly constituted." This is well exemplified in the photograph and description of one of our cases (fig. 5).

Keibel and Mall [35] considered the papillae of Retzius as artefacts, but our illustration (fig. 11) regarding the heterotopias appears to contradict their assumption. We believe that the papillae are normally present, and the way in which they are formed by the proliferation of the outer layer of the neuroblasts is fairly evident. It raises the question whether or not Brunschweiler's theory, that the cerebral cortex is a diffuse heterotopia, is correct. We are inclined to agree with his conclusion.

In order to stimulate further research and interest and to try to solve one of the most interesting of teratologic enigmas, we present detailed clinicopathologic studies of two additional cases of microcephalia vera. The first brain illustrates the agyric form, the second the complex microgyric form.

REPORT OF CASES

Case 1.—*Absence of cerebral convulsions, agyria.*

D. F., a girl, was born in September 1924 and died in October 1926.

The specimen was sent by Dr. L. S. Dudgeon of St. Thomas' Hospital. The clinical notes contained little reference to the mental and neurologic condition of the child, but the inference from the available records is that at first the condition

34. Sachs, B., in Abt, Isaac A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1923, vol. 2, p. 407.

35. Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2.

approximated one of decerebrate rigidity and that later the reflexes were lost. No abnormality was noted during pregnancy or at birth, except that the head was retracted. The child had pneumonia at 3 weeks of age and at 9 weeks was admitted to the Victoria Hospital for Children, Tite Street, on account of persistent arching of the back since birth. The limbs were then noted to be spastic, with exaggeration of the deep reflexes. The circumference of the head was 12½ inches (31.12 cm.). The pupils at that time reacted to light. At the age of 5 months the child had three convulsions in two weeks, the longest fit lasting twenty minutes. She was admitted to St. Thomas' Hospital in March 1925, under Dr. Jewesbury; it was noted that she lay in the "gun-hammer" position of extreme opisthotonos. The pupils were inactive, and the child appeared to be blind. The eyes rolled continuously, and sometimes there was strabismus. The knee jerks were absent, the plantar responses present (type not stated). A lumbar puncture gave clear fluid under pressure, with no excess of cells or globulin. The Wassermann and Sachs-Georgi reactions of the fluid were negative. Roentgenograms of the skull and cervical portion of the spine showed no abnormality.

The child was readmitted to St. Thomas' Hospital in July 1925, suffering from gastro-enteritis, from which she quickly recovered. No alteration in the physical signs was noted at that time. She was admitted again in October 1926 with bronchopneumonia, from which she died.

The specimen received consisted of the left cerebral and cerebellar hemispheres and half of the brain stem. It weighed 170 Gm. Figure 1 shows that there was almost complete absence of sulci, although the principal fissures, i. e., the rolandic calcarine and parieto-occipital, were indicated by shallow grooves. The fissure of Sylvius was short, scarcely reaching beyond the origin of the fissure of Rolando, and there was no island of Reil. On the inner and inferior surfaces of the frontal lobes the sulci were, however, deeper, and the orbital sulcus had the normal H shape. The olfactory sulcus was also represented.

On section of the brain (figs. 2 and 3) the most striking feature was the great width of the cortical gray matter, which in many places was over 1 cm. thick and was everywhere quite disproportionate to the small centrum semiovale. The basal ganglia, brain stem and cerebellum had a nearly normal appearance, but all the ventricles were considerably dilated.

Histologic examination of the cerebral cortex showed a large number of nerve cells and fibers throughout. These were more widely spaced than in the normal cortex, and it was impossible to make out any definite lamination. Many of the cells were somewhat rudimentary in appearance, containing very little cytoplasm, but some were quite well differentiated, with large cell bodies and definite Nissl granules. In addition, some large irregular ganglion cells were seen, which resembled those in tuberous sclerosis. Myelinization was fairly well advanced both in the cortex and in the white matter, although it was much less than is normal for the age of 2 years. It was noteworthy that the radial fibers were fairly abundant in the cortex forming the lips of the groove which represented the fissure of Rolando, whereas in the frontal and occipital poles they were very sparse. Throughout the cortex, however, there was a fairly well developed layer of tangential fibers immediately under the surface. The hippocampus had the normal conformation, and its nerve fiber layers were well myelinated. The temporal cortex in its immediate neighborhood was somewhat better myelinated than most regions of the cortex. The neuroglia cells showed no abnormality, and there was little, if any, increase of neuroglia fibers in the white matter. Staining

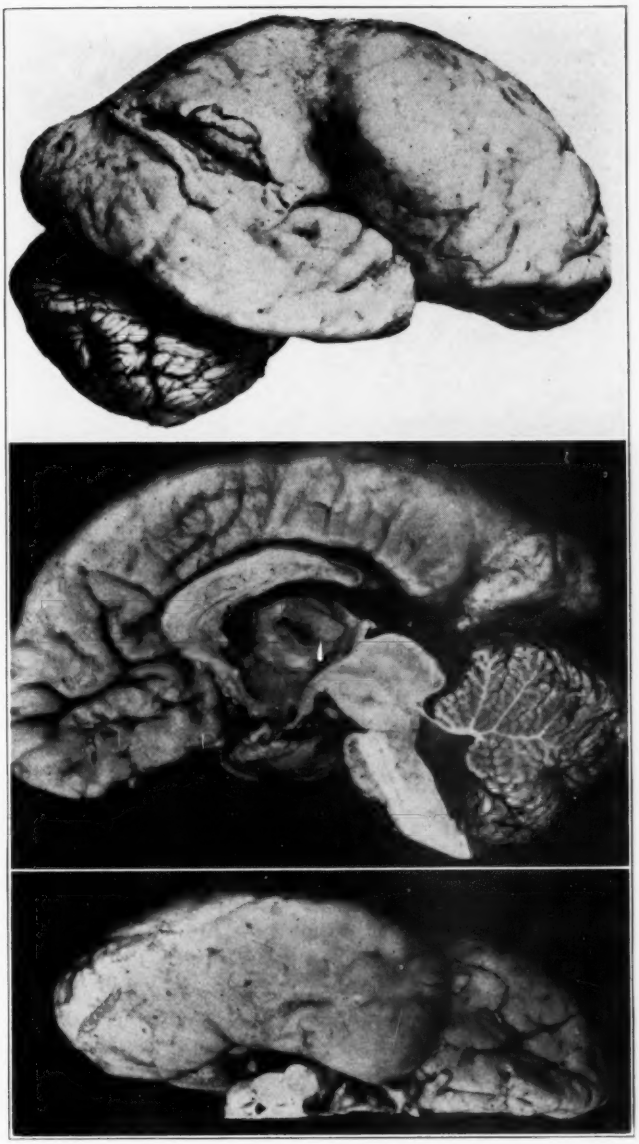

Fig. 1 (case 1).—Agyric microcephaly. External appearance of the right half of the brain.

Fig. 2 (case 1).—Agyric microcephaly. Note the very thick cortex and the thin zone of white matter.

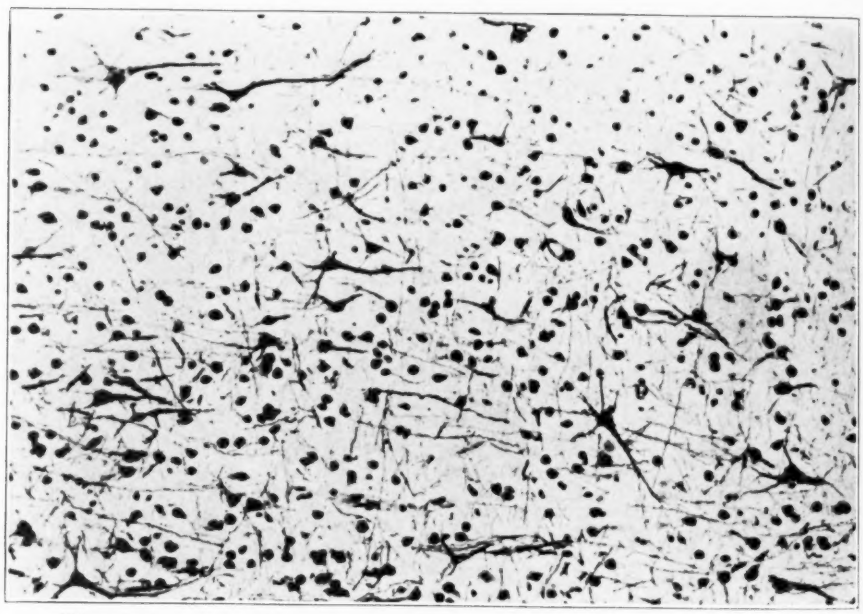

Fig. 3 (case 1).—Agyric microcephaly. Section of the cereberal cortex (Bielschowsky's stain).

with scarlet red did not reveal any degeneration of myelin or abnormal lipoid. In the basal ganglia the nerve cells appeared to be fairly normal in type and distribution.

In the midbrain there was a thin band of fibers in the outer part of the crus representing the pyramidal system, with probably also some fibers from the temporal lobe. There was some irregularity of the myelinated fibers around the

Fig. 4 (case 1).—Agyric microcephaly. Cross-section of the midbrain (Weigert-Pal's stain). Note the irregularity of the white fibers around the iter of Sylvius.

iter of Sylvius (fig. 4), which did not form a smooth curve round the gray matter but projected inward as two tongues of obliquely directed fibers. The other fiber systems in this region were normally arranged. In the pons the chief abnormality was in the arrangement of the pyramidal fibers, which passed through as a solid bundle overlaid by the transverse fibers forming the middle peduncle. The cerebellar cortex was almost normal; the molecular layer appeared rather thin, but there was no loss of Purkinje or granule cells, or any neuroglial overgrowth. The dentate nucleus was, however, irregularly arranged, appearing as

a confused mass of cells, with little of the usual appearance of a convoluted layer. The individual nerve cells, however, as well as the fibers of the superior cerebellar peduncle, were normal.

In the medulla the chief abnormality was in the disposition of the inferior olive (fig. 5), which was broken up into three or four rounded nuclei, which lay in a chain along the line from the vestibular nuclei to the normal position of the olive. In consequence of this arrangement the system of the mesial fillet was spread out laterally in a wider band than normal.

The cranial nerves and their nuclei were normally represented. The pyramidal system was considerably smaller than normal and consisted of rather thinly

Fig. 5 (case 1).—Agyric microcephaly. Cross-section of the medulla oblongata (Weigert-Pal's stain), showing heterotopia of the olive.

myelinated fibers. It was broken into a smaller superficial and a larger deep portion of bundles of superficial arcuate fibers.

CASE 2.—*Complex microgyria with microcephaly—"chestnut" brain.*

Dr. Norah Schuster furnished the specimen in this case. The brain was that of a boy, E. S., aged 3 months, who died in the Infants Hospital, Vincent Square, in 1928. He was admitted for fits, which occurred about six times a day. He did not appear to see and could not follow a light. He died of subacute meningitis. The Wassermann reaction of the blood was normal.

The brain weighed 14 ounces (396.9 Gm.) when removed.

In this case the right cerebral hemisphere and the cerebellum and brain stem (fig. 6) down to the lower end of the pons were received. The cerebral hemi-

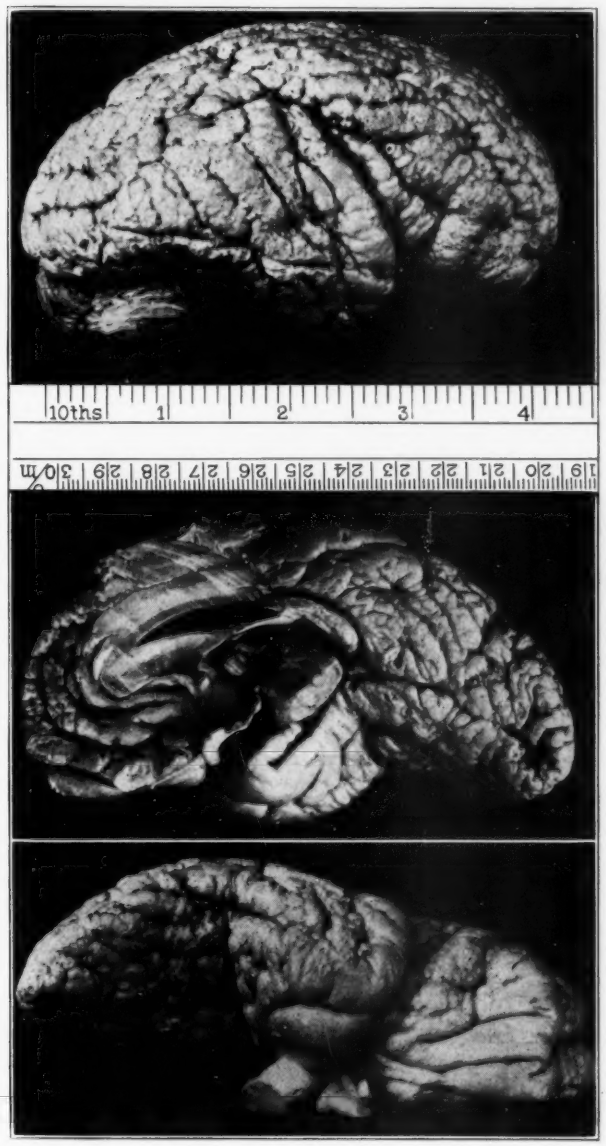

Fig. 6 (case 2).—Complex microgyria. External view of the brain.

sphere weighed 112 Gm. and the cerebellum 47 Gm. The appearance of the cerebral hemisphere was unusual, the surface over its external convexity being irregularly wrinkled, with numerous small bosses and depressions. There were also deeper sulci, a few of which lay in the normal positions. The calcarine, parieto-occipital, superior temporal, orbital and olfactory sulci were represented, as well as the anterior parts of the callosomarginal sulcus and collateral fissures. The fissure of Rolando was represented by a shallow depression, and there was no trace of precentral or postcentral sulci. The deeper fissures over the convexity tended to run in an anteroposterior direction. While almost all the parts of the cortex showed a wrinkled appearance, very like that of a chestnut kernel, the orbital, hippocampal and superior temporal convolutions were smooth and of almost normal appearance.

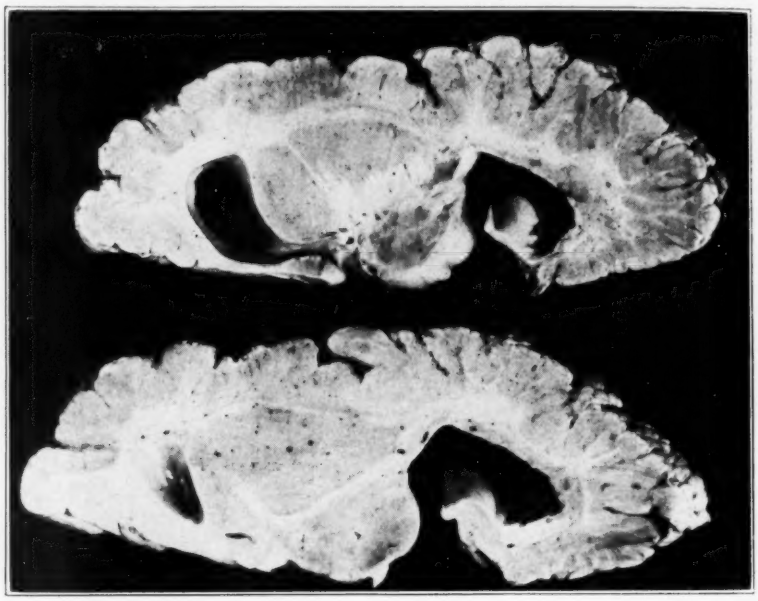

Fig. 7 (case 2).—Horizontal section of the brain, showing the general thickness and the complex convolutions of the cortex.

On section of the brain (fig. 7) the superficial wrinkling was seen to be due to a complex arrangement of the layer of nerve cells, which was twisted and convoluted in an intricate manner within the substance of one of the larger gyri marked out by the deeper sulci. This can best be understood by reference to figure 8, which shows that the nerve cells lay in a rather thin layer, overlaid by a more acellular layer of neuroglia cells and fibers (Randschleier). In the deeper parts of the gyrus the apposed surfaces of this superficial molecular layer were fused, the line of fusion being indicated by the presence of large blood vessels surrounded by a dense zone of neuroglia fibers (fig. 9).

Examination of the neuronal layer under a higher magnification (fig. 10) showed that the great majority of the nerve cells were in a primitive condition, having a small oval cell body and indefinite Nissl granules. They differed little from neuroblasts. In some places, however, larger, more differentiated pyramidal

Fig. 8 (case 2).—Section of the cerebral cortex stained with iron hematoxylin and showing the complex arrangement of the cortical layer of neurons.

Fig. 9 (case 2).—Section of the cortex under low magnification, showing how the larger vessels lie in the center of the fused marginal veils. The extreme thinness of the cortical layer of neurons is also shown.

cells were seen. There was some attempt at lamination, but as the layer of nerve cells was very narrow and most of the cells were very small it was impossible to correlate these layers with those of the normal cortex. The white matter was considerably encroached on by the convolutional complexity of the cortex, which in many places was more than 1 cm. in thickness. Myelinization was beginning here and was about as far advanced as would be expected at this age (3 months). There was, however, throughout the white matter a close feltwork of neuroglia fibers, and many isolated and rather thicker fibers were seen in the cerebral cortex. In the superficial molecular layer there was also considerable gliosis, especially around the vessels and where the layer was in contact with the meninges. In the pia mater there was a considerable excess of large macrophage cells as

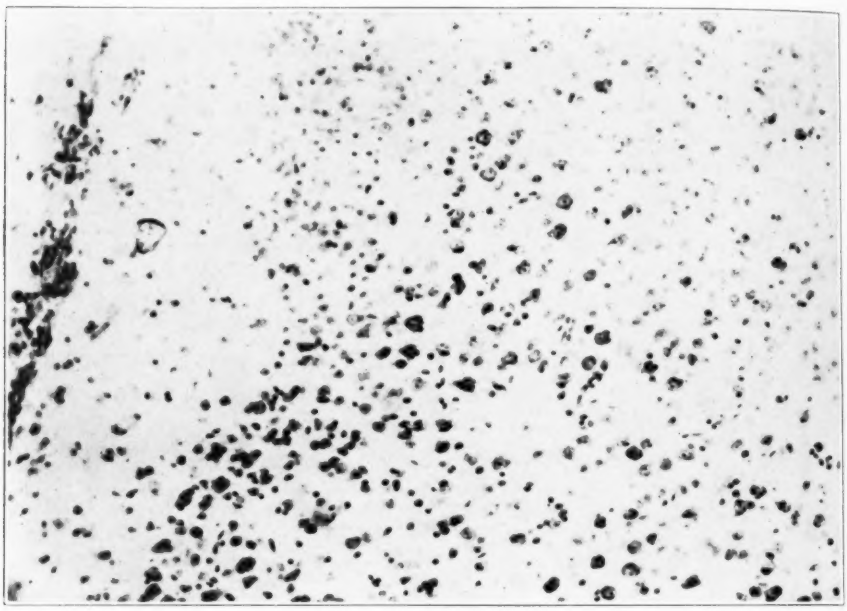

Fig. 10 (case 2).—Higher magnification of a section of the cortex (Nissl's stain), showing the primitive nature of the nerve cells.

well as a smaller number of lymphocytes. No polymorphonuclear leukocytes were seen, however. The ventricles were somewhat dilated. The basal ganglia appeared normal both macroscopically and microscopically, although here also the nerve cells were undeveloped. Staining with scarlet red revealed a considerable amount of lipoid in the processes of macroglia cells in the white matter of the brain, but this is probably the normal condition during the process of myelinization.

Examination of the brain stem showed nothing abnormal for this stage of development except that myelinization of the pyramidal tracts had not commenced. In the cerebellum also the conditions were those normal for the age of 3 months. There was still a thin layer of granule cells on the surface of the molecular layer, and many microglia cells containing lipoid were seen in the molecular and granular layers. Myelinization of the white matter of the cerebellum was well advanced.

COMMENT

The two types of maldevelopment which these brains presented in an almost pure form are not rare in localized areas in microcephalic brains. Although at first sight there are certain similarities between the two types, for example, the wide zone occupied by the gray matter of the cortex, it seems to us that they are essentially distinct both in their characters and in their mode of development. The most noteworthy difference is in the arrangement of the nerve cells of the cortex, which in the first case were spread diffusely through a thickness of about 1 cm., whereas in the second they were arranged in a convoluted lamina which was never more than 1 mm. in thickness.

It is natural to seek an explanation of these anomalies along the lines of development. In a full report on a microcephalic brain, remarkably similar to that in our first case, Brunschweiler explained the thickness of the cortex as a diffuse heterotopia. His argument in general was: During the third and fourth months of fetal life the nerve cells are passing across the brain substance from the germinal layer or matrix, which lies under the walls of the ventricles, and are crowding toward the surface, where during the fourth month they form a dense but shallow layer of neurons. This is separated from the surface by a molecular marginal layer (marginal veil of His) which is free from neurons. In agyric microcephaly this dense neuronal layer is never formed, since the neurons halt on their passage at some distance from the cortex. According to some writers it is the crowding of the neuroblasts in the cortical neuronal layer and their gradual separation from one another which necessitate the formation of convolutions. It is a natural corollary to this theory that when a cortical layer is not formed during the fourth month of fetal life the necessity for convolutions does not arise.

Brunschweiler [13] mentioned a similar failure of migration, causing a more obvious heterotopia, in the condition of the inferior olive. This he found broken up into several fragments which lay in the line along which its cells migrate from the rhombic lip, where they originate (Elliot Smith [36]), to the junction of the median fillet and pyramidal tracts.

This explanation is certainly reasonable but appears to us to leave one factor out of account. It is well known that in nonconvoluted brains, such as that of the rabbit, the cortical nerve cells are much more closely packed together than in the human brain. It appears indeed as though the more fully differentiated nerve cells in the convoluted brains needed more room than those of lower mammals. This need for the separation of nerve cells from one another may have been a factor

36. Smith, G. Elliot, quoted by Cunningham, Daniel John: Text Book of Anatomy, ed. 6, New York, William Wood & Company, 1931.

in determining the great thickness of the cortex in case 1. It is true, however, that the nerve cells in this brain were considerably farther from one another than they are in the normal cortex, the only place where they were arranged close together being in the hippocampus.

In the brain in case 2, on the other hand, the thin convoluted layer of nerve cells, covered with a fairly wide marginal veil, suggests that the migration of the neurons to the surface had taken place normally. From this stage, however, development proceeded along abnormal lines. Either during the stage of formation of the main sulci, i. e., during the fifth and sixth months, or before this, the need for expansion caused this layer to become convoluted within the substance of the brain, but the further development of the neuronal layer and its differentiation into the various cortical layers failed to take place. It seems clear that the convoluted pattern of this layer was formed before the pia and arachnoid were differentiated from one another, since the pia mater did not follow the lines of the marginal zone. It did, however, dip into the main sulci, which correspond more or less to the more primitive sulci. In a brain at the twentieth week of fetal life which we examined, which showed the early stages in the formation of sulci, the pial layer of mesodermal cells was seen to follow the lines of the cortex to the bottom of the sulci. According to Keibel and Mall, the separation of the pia from the arachnoid takes place at about the nineteenth week, which agrees with this observation. This seems to indicate that the error of development in the cortex in case 2 occurred at a period not later than the end of the fourth month of fetal life.

It is impossible to suggest any reason that the convoluted arrangement of the neuronal layer should be associated with the absence of further differentiation of the cortex into its several layers and of separation of the neurons from one another. Nor is it clear why this error of development should be associated with a great increase of neuroglia fibers throughout the cerebral hemispheres. It may, however, be interesting to correlate this lawless attempt at expansion of the neuronal layer with the formation of the papillae of Retzius, which normally takes place about the end of the fourth month, thus immediately preceding the formation of sulci. If one examines a brain of this age with the naked eye one sees numerous small papillae on its surface, especially over the occipital pole. Under the microscope (fig. 11) these papillae are seen to consist of outgrowths of masses of neuroblasts through the marginal veil. In other places the marginal veil appears to dip irregularly into the cortical neuronal layer, as though in the process of growth the latter were becoming bent and convoluted. After the convolutions form, all trace of these papillae is lost. The lawless expansion of the cortex comes for a time under the rule of law, finding an outlet in the wide increase in cortical area which the

main convolutions provide. Later, however, these become insufficient to accommodate the growing cortex, and an irregular and unsystematized growth again takes place in the formation of the secondary convolutions. There are also close analogies between the convoluted pattern of the nerve cells in the cortex in this case and those in the cerebellar cortex and the nuclei of the cerebellum.

There is little in either of the brains examined which helps one to decide the much disputed question of the cause of cerebral maldevelopment. Nor can one trace the developmental processes with any degree of accuracy, apart from establishing to some extent the time at which the first error took place.

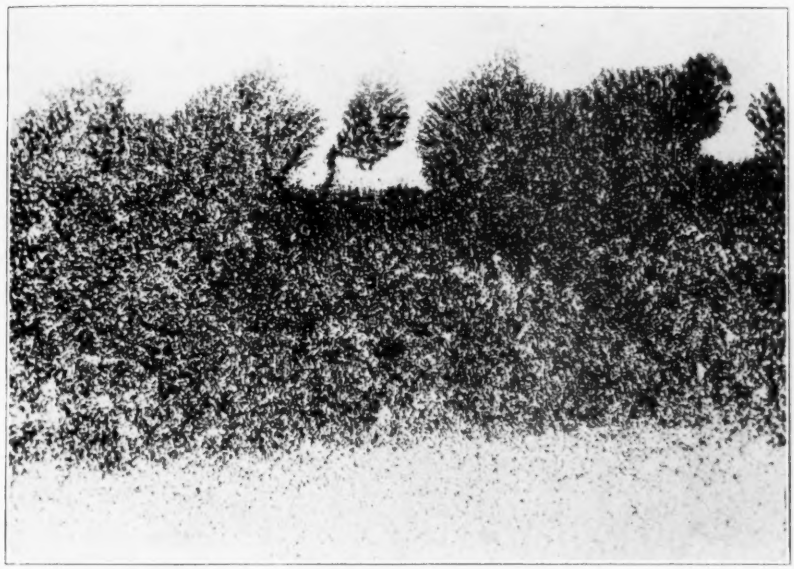

Fig 11.—Section of the cerebral cortex of a 20 week fetus (occipital pole) showing papillae of Retzius, or projections of the cortical layer of neuroblasts into the marginal veil. The outer border of the acellular marginal veil is not seen in the photomicrograph.

The two brains provide typical instances of the laws of "retardation" and "propulsion" in maldevelopment, on which Jelgersma [37] laid stress. The condition in case 1 is well explained by the hypothesis of "retardation," or slowing down of the tempo of development during the third and fourth months of fetal life. In case 2, on the other hand, there was at about the same age, or a little later, a "propulsion" or quickening of the tempo, whereby the cortical layer of neuroblasts expanded laterally before the sulci had time to form and so became convoluted within

37. Jelgersma, H. C.: Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:83, 1930.

the thickness of the cortex. It would be possible on the same theory to consider the excessive gliosis of this brain as a premature aging, but we are more inclined to look on the formation of neuroglia fibers as a reaction to local chemical or mechanical stimuli. It is, however, interesting to recall that this gliosis allies the complex microgyric type of microcephalic brain to the normally convoluted microcephalic brains with excessive gliosis which Freeman [33] has described.

SUMMARY AND CONCLUSIONS

Two different forms of microcephalia vera, the agyric and the complex microgyric forms, depending on two different types of anomaly, are described. The anomalies, however, are of the same generic kind.

One conclusion that can be formulated from the study and examination of these brains and from the published reports is that the underlying pathologic processes were at work before the fourth month of fetal life.

The teratologic defects resulting from these pathologic factors involved principally the cortex of the cerebral hemispheres, where arrest of cerebral development was the essential observation.

Heterotopias of the cerebral cortex and of the olive were striking evidences of the embryologic anomaly.

It is evident that not one but many diverse factors which can affect the germ cell or the young embryo may produce microcephalia vera.

Clinical Notes

AMYOTONIA CONGENITA WITH FAMILIAL INCIDENCE

SAMUEL HURWITZ, M.D., AND MARK GERSTLE JR., M.D., SAN FRANCISCO

Since the first descriptions of amyotonia congenita by Oppenheim,[1] Batten[2] and Berti,[3] about two hundred cases of this disease have been reported. The criteria for diagnosis are: (1) onset early in life, (2) remarkable muscular flaccidity and loss of power, chiefly in the lower extremities; (3) absence or diminution of tendon reflexes; (4) absence of apparent muscular atrophy; (5) quantitative diminution of electrical reactions but absence of reaction of degeneration, and (6) normal mentality and sensation. Males and females are about equally affected. The symptoms are noted at or soon after birth in over 80 per cent of cases (Faber[4]). Early writers stressed the nonfamilial character of the disease, but more recently numerous familial examples have been noted (Foot,[5] Reuben,[6] Allaben,[7] Gurdjian[8]).

Oppenheim[1] and Spiller,[9] who reported the first observations at autopsy, believed that the disease was due to arrested development of the muscle tissue. Baudouin,[10] on the other hand, thought that the cord was primarily involved. Fetal or infantile poliomyelitis was stated to be the etiologic factor by Bernhardt

From the Departments of Pediatrics and Medicine (Division of Neurology), University of California Medical School, and the Department of Public Health of San Francisco.

1. Oppenheim, H.: Ueber allgemeine und localisierte Atonie der Muskulatur (Myatonie) im frühen Kindesalter, Monatschr. f. Psychiat. u. Neurol. **8**:232, 1900.

2. Batten, F. E.: Three Cases of Myopathy, Infantile Type, Brain **26**:147, 1903.

3. Berti: Contribuzione all 'atonia muscolare congenita di Oppenheim, Pediatria **13**:134 (Feb.) 1905.

4. Faber, H. K.: Amyotonia Congenita: A Survey of the Known Cases with a Report of Three New Cases, Am. J. Dis. Child. **13**:305 (April) 1917.

5. Foot, N. C.: Report of a Case of Amyotonia Congenita with Autopsy, Am. J. Dis. Child. **5**:359 (May) 1913.

6. Reuben, M. S.: Amyotonia Congenita of Oppenheim: A Report of Six Cases, with a Full Review of the Literature, Arch. Int. Med. **20**:657 (Nov.) 1917.

7. Allaben, G. R.: Two Cases of Amyotonia Congenita Occurring in the Same Family, J. A. M. A. **83**:842 (Sept. 13) 1924.

8. Gurdjian, E. S.: Myatonia Congenita with Particular Reference to Pathology and Familial Tendency, Arch. Neurol. & Psychiat. **24**:52 (July) 1930.

9. Spiller, W. G.: Generalized or Localized Hypotonia of the Muscles in Childhood (Myatonia Congenita), Univ. Penn. M. Bull. **17**:342, 1904-1905.

10. Baudouin, A.: La myatonie congenitale (maladie d'Oppenheim), Semaine méd. **37**:241, 1907.

and by Marburg.[11] Gurdjian [8] was inclined toward a toxic fact... involving the neuromuscular system, with perhaps an underlying familial predisposition of this system to the "deleterious effects of the toxic causes." He concurred with Greenfield and Stern [12] that amyotonia is only a subgroup of the Werdnig-Hoffmann paralysis. Primary abiotrophy of the musculature with a secondary failure of proper development of the whole nervous system was the pathogenesis proposed by Reuben.[6] Faber [4] expressed the belief that the original fault lay in a defective germ plasm of reproductively exhausted parents, with the primary lesion congenital hypoplasia of the lower motor neuron, the changes in the muscles being secondary.

Pathologic changes have been described in all the skeletal muscles and in the whole cerebrospinal system, depending on the severity and duration of the disease. The muscles are usually pale and flabby, and small fibers predominate with an occasional hypertrophied fiber. There are an increase in intermuscular fat and connective tissue and an apparent augmentation of the sarcolemmic nuclei. The motor cells of the anterior horns are reduced in number; the peripheral nerves are decreased in size and show deficient myelinization, with the end-plates visible in only a few cases. The cord may be diminished in caliber, and the cord tracts may show deficient myelinization. The cerebrum, medulla and cerebellum are only occasionally involved, and a diminution in the number of motor cells of the cortex and cranial nuclei has been reported. Vascular changes due to a marked thickening of the adventitia of the blood vessels have been observed.

Few metabolic studies have been made in cases of amyotonia congenita. Gittings and Pemberton [13] found lowered excretion of creatinine, which was confirmed by Ziegler and Pearce.[14] The latter demonstrated lowered excretion of chloride but no disturbance of the values for calcium, phosphorus or uric acid.

Prognosis for recovery is extremely poor, and no case of complete recovery has been reported. Reuben reported forty-five deaths in eighty-four cases, with twenty-nine deaths among forty-two infants before the age of 1 year. Respiratory infections have accounted for about 90 per cent of the mortality (Faber).

The efficacy of any therapy in a disease such as this in which there is a natural tendency to improvement is difficult to evaluate. Thyroid, epinephrine, tonics, electrical stimulation and massage have all been tried with varying results. However, the great number and variety of remedies advocated are sufficient proof that no adequate therapeutic agent has as yet been found.

REPORT OF A CASE

History.—E. S., a white girl aged 6 years, was admitted to the hospital on Feb. 7, 1934, because of otitis media and mastoiditis on the left side. She had been admitted twice previously for pneumonia, the last time just two months before the present admission. She was born at term, and delivery was normal. Development was thought to be normal until the age of 14 months, when she

11. Marburg, O.: Zur Klinik und Pathologie der Myatonia Congenita, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **19**:133, 1911.

12. Greenfield, J. G., and Stern, R. O.: The Anatomical Identity of the Werdnig-Hoffmann and Oppenheim Forms of Infantile Muscular Atrophy, Brain **50**: 652, 1927.

13. Gittings, J. C., and Pemberton, R.: Metabolic Observations on Amyotonia Congenita, Am. J. M. Sc. **144**:732 (Nov.) 1912.

14. Ziegler, M. R., and Pearce, N. O.: A Metabolic Study of Amyotonia Congenita, J. Biol. Chem. **42**:581 (July) 1920.

started to stand but would not attempt to walk. At a clinic, thyroid therapy was prescribed for six months, without apparent benefit.

The father, aged 43, and mother, aged 36, were alive and well. The father's six brothers and two sisters were well, but the first child of one sister had generalized muscular weakness, never sat up or walked and died of pneumonia at the age of 2 years. In addition, a brother and sister of the patient were both in the San Francisco Hospital; their records disclose the characteristic signs of amyotonia congenita, which was the diagnosis made by the attending physician in each case; they died of respiratory infections at 3½ and 7 years of age, respectively. Two other children of the family, a girl aged 9, and a boy aged 3, were examined by us and found to be normal.

Examination.—The patient was well nourished and of normal mentality, with a rather large head; she lay flat in bed, unable to raise herself to a sitting position.

Fig. 1.—Photograph of the patient at the age of 6. Note the normal muscular development with no apparent atrophy.

The face was full and expressionless, and the neck was very short. The skin was attached to the underlying tissues, and the muscles could not be felt apart from the subcutaneous fat, which was well developed throughout. In the sitting posture slight kyphosis was apparent. The breathing was entirely abdominal, and the rate was occasionally rather rapid (from 30 to 40). Athetoid movements of the hands were observed. Sphincter control and sensory reactions were normal. There was generalized hypotonia of the entire musculature, which was most marked in the lower extremities; the child was unable to hold the head upright, stand or walk. Speech was preserved, and the cranial nerves were not involved. The abdominal reflexes were equal and active, but all deep reflexes were abolished. No pathologic reflexes were elicited. Both nerves and muscles showed diminished reaction to galvanic and faradic current, but no reaction of degeneration was demonstrable.

Laboratory Examination.—Chemical analysis of the blood on two occasions revealed the following values:

	3/20/1934	4/1/1934	Normal
	Mg. per 100 Cc.		
Calcium	10.45	10.55	10 to 12
Phosphorus	6.25	6.37	4 to 5
Creatine	4.0	....	3 to 5
Creatinine	1.20	....	1 to 2
Chloride (sodium chloride of serum)	533.2	....	500 to 600
Magnesium (plasma)	2.66	....	2 to 3
Magnesium (red blood cells)	5.42	....	6.5 to 7.2

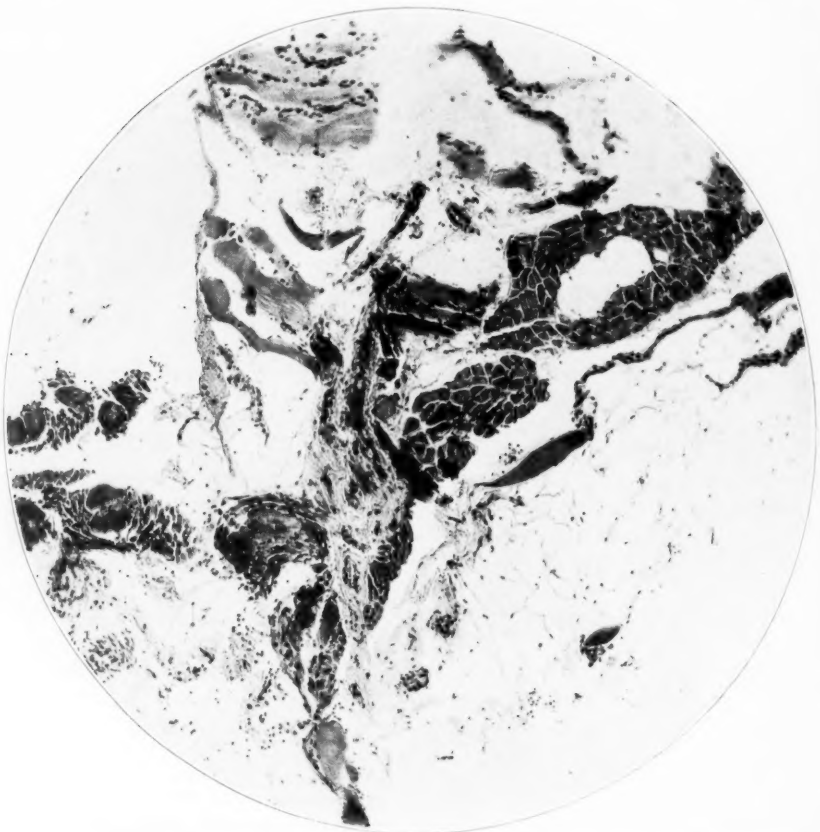

Fig. 2.—Photomicrograph (× 105) of a section of the gastrocnemius muscle. The muscle fibers are paler than normal with a predominance of small ones. The sarcolemmic nuclei are preserved where the fibers have almost disappeared. There is an increase in perimuscular fat.

A twenty-four hour specimen of urine with a volume of 1,200 cc. showed 313 mg. of creatine and 250 mg. of creatinine. A similar specimen from a child used as a control (of the same age and weight and receiving a similar diet) showed 78 mg. of creatine and 442 mg. of creatinine.

The spinal fluid was normal. The Wassermann test was negative for the patient and for her parents. The blood grouping for the patient and her family was as follows: patient, type *2*; father, type *2*; sister who died of amyotonia, type *2*; mother, type 4; other two siblings, type 4. The basal metabolic rate was +9 per cent (Benedict).

The test for dextrose tolerance, carried out on venous blood, gave the following results on two occasions:

	March 20	April 3
	Mg. per 100 Cc.	
Fasting	109.9	112.4
½ hour	141.8	198.1
1 hour	109.9	177.0
2 hours	112.4	144.9
3 hours	133.3	170.9

Roentgenograms.—Those of the skull and the lumbar and sacral portions of the spine revealed a normal picture. The bone age was normal; the slight rarefaction noted was probably due to disuse. The diaphragmatic movement was slight; there was hilar congestion.

Biopsy of the Gastrocnemius Muscle.—The material consisted of a very small piece of pale, doughy, flabby, yellowish-white tissue. On section an increase in the perimuscular fat was seen (fig. *2*). The muscle fibers were paler than normal, with a marked disproportion in the size of the fibers and a predominance of small ones. There appeared to be an increased cellularity due to the sarcolemmic nuclei, the latter often being preserved where the fibers had almost disappeared. The cross-striations were demonstrated with difficulty.

COMMENT

This case is a typical example of amyotonia congenita, fulfilling all the required diagnostic criteria previously outlined. In differential diagnosis, Werdnig-Hoffmann's spinal progressive muscular atrophy and muscular dystrophy must be considered. The latter is characterized by onset during childhood rather than in infancy; atrophy is definite although pseudohypertrophy or actual hypertrophy is an early and prominent symptom in one variety, and the spinal cord and peripheral nerves show no pathologic changes. In muscular atrophy of the Werdnig-Hoffmann type the pelvic girdle and muscles of the small of the back are first affected; atrophy is present, and there is a reaction of degeneration, while rapid deterioration with early death is common.

A definite and striking familial incidence was shown in the case reported here which emphasizes the fact that the earlier opinion of a nonfamilial tendency must be revised. Beevor [15] reported four cases in one family, Gurdjian noted the condition three times in one family of six children, and Reuben described the disease in three sisters. Amyotonia has been recorded in twins by Pearce [16] and Forbus and Wolf.[17] The latter authors observed identical twins affected at the fifth month who ultimately died and were examined post mortem. They believed that the etiologic factor was a maldevelopment of the ovum.

15. Beevor, C. E.: A Case of Myatonia Congenita, Proc. Roy. Soc. Med. (Sect. Neurol.) **1**:1, 1907-1908.

16. Pearce, N. O.: Amyotonia Congenita, Am. J. Dis. Child. **20**:393 (Nov.) 1920.

17. Forbus, W. D., and Wolf, F. S.: Amyotonia Congenita (Oppenheim's Disease) in Identical Twins, Bull. Johns Hopkins Hosp. **47**:309 (Dec.) 1930.

A most interesting observation which, to our knowledge, has not been recorded previously is the blood grouping. The blood of the father and that of the two affected children for whom groupings were made belonged to the same class, namely, type 2. Because of the fixed inheritance of the blood groups according to the mendelian law, it is suggested that amyotonia may be found most frequently in persons whose blood is of type 2 and may in some cases be hereditary. Verification by future reports will be awaited with interest.

The age of the parents and the fact that this was the fourth pregnancy lend some support to Faber's theory of reproductive exhaustion. In a series of 16 cases he noted that 53 per cent of the patients were born of the fourth or a later pregnancy and concluded that the original fault in Oppenheim's disease was a defective germ plasm of reproductively exhausted parents.

The repeated pneumonic attacks illustrate the definite predisposition of these patients to respiratory infections. All authors have agreed that the greatest single factor in the mortality of persons with amyotonia congenita is a disease of the respiratory tract, which, according to Faber, causes 90 per cent of all the deaths.

The similarity of the pathologic picture of Werdnig-Hoffmann's paralysis to that of Oppenheim's disease is emphasized by the pathologists' inability to make a definite diagnosis from biopsy material alone. Greenfield and Stern, after a review of all the recorded autopsy reports, concluded that the two diseases show anatomic identity of pathologic changes. They expressed the belief that Werdnig-Hoffmann paralysis represents a more advanced stage of involvement of the nervous system. However, the similarity of pathologic observations does not signify that the conditions are alike clinically.

Metabolic studies revealed a lowered excretion of creatinine, substantiating the findings of Gittings and Pemberton. In addition, there was an elevation of the phosphorus content of the blood which has not been previously reported. A possible explanation is that in some cases enlargement of the thymus has been noted with Hassal's corpuscles greatly developed (Rothmann[18]); Martinetti[19] has shown recently that thymus extract may elevate the phosphorus content of the blood. The first report of the magnesium content of the blood in a case of amyotonia congenita is reported here. At present, however, we are unable to interpret the significance of the lowered value for red cell magnesium.

Thyroid therapy, advocated by Kerley[20] and others, proved entirely without effect on our patient. As has been stated previously, the natural tendency of the disease is toward improvement, which makes it extremely difficult to estimate the value of any therapeutic agent. Since the blood chemistry seemed to indicate an inability of the body to convert creatine to creatinine, it suggested the use of glycine, as has been advocated for progressive muscular dystrophy.[21] After three months with this therapy the parents stated that there was improvement in the patient's appetite and that she had remained free from infection, though examination revealed no change in the neurologic status. A much longer period of observa-

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18. Rothmann, M.: Ueber die anatomische Grundlage der Myatonia Congenita. Monatschr. f. Psychiat. u. Neurol. (supp.) **25**:161, 1909.

19. Martinetti, N.: Influence of the Thymus on the Phosphorus Content of the Blood, Riv. di clin. pediat. **31**:163 (Feb.) 1933.

20. Kerley, C. G., and Blanchard, K.: Amyotonia Congenita: Report of Two Cases, Arch. Pediat. **44**:26 (Jan.) 1927.

21. Milhorat, A. T.; Techner, F., and Thomas, K.: Significance of Creatine in Progressive Muscular Dystrophy and Treatment of This Disease with Glycine. Proc. Soc. Exper. Biol. & Med. **29**:609 (Feb.) 1932.

tion will be required to determine the efficacy of glycine therapy, but in view of our metabolic findings it appears to have a rational biochemical basis for therapeutic application in amyotonia congenita.

SUMMARY AND CONCLUSIONS

A case of amyotonia congenita with striking familial incidence is described in detail.

A similarity of blood grouping (type 2) between the father and the affected children is reported for the first time.

Metabolic studies revealed increased values for blood phosphorus and lowered values for red cell magnesium and confirmed the lowered excretion of creatinine previously recorded.

The use of glycine for treatment of amyotonia congenita is suggested.

TUMOR OF THE PINEAL GLAND (PINEALOCYTOMA) WITH MENINGEAL AND NEURAL METASTASES

E. D. Friedman, M.D., and Alfred Plaut, M.D., New York

The case we are reporting is unusual and in some respects seems to be unique. The problem it presented to the clinician and the pathologist was finally solved by microscopic study of the tissues obtained post mortem.

REPORT OF A CASE

History.—The patient, a hatter, aged 33, on admission to the hospital on Jan. 20, 1933, complained chiefly of pains in the back, numbness of the hands and progressive weakness and numbness of the right thigh. The family history was irrelevant. In 1929 the patient had suffered from polyuria, polydipsia, blurring of vision and loss of sexual power. He was observed at the Mount Sinai Hospital, where a diagnosis of tumor of the pituitary gland was made (a flattened sella turcica was found) and roentgen therapy was instituted. At that time the basal metabolic rate was —29. The blurring of vision improved sufficiently to permit him to return to work. The diabetes insipidus disappeared, but potency did not return. He worked at his trade until three weeks prior to admission in 1933. He then had what was described as a cold, with coryza and backache but no fever. The backache was worse on stooping or bending and within a few days was followed by numbness of the right hand. A week later paresthesia of the left hand developed. The paresthesias continued up to the time of admission. Finally he was compelled to go to bed because of the numbness and the progressive weakness of the right thigh.

Physical Examination.—The patient appeared pale and seemed younger than his given age. The genitalia were underdeveloped. There were scant hirsuties on the face and trunk, a female type of pubic hair and a distribution of fat which was typical of a disorder of the pituitary gland. The blood pressure was low, 90 systolic and 50 diastolic. The blood count showed: hemoglobin, 85 per cent; red cells, 4,770,000; white cells, 8,800; polymorphonuclears, 70 per cent; lymphocytes, 21 per cent; monocytes, 4 per cent; eosinophils, 2 per cent and staff cells, 3 per cent. Chemical analysis of the blood showed: sugar, 100 mg. per hundred cubic centimeters, and nonprotein nitrogen, 33 mg. The Wassermann test of the blood was negative.

Neurologic examination showed weakness of all the extremities, more pronounced on the right side; the upper extremities were more involved than the lower; the deep reflexes were absent in the lower extremities and diminished in the upper; the abdominal reflexes were brisk; there was no Babinski sign; slight sensory changes were present distally and there was loss of faradic response in the muscles of the thighs. There was a diminution of the sense of smell and in visual acuity; bilateral optic atrophy was present; the right pupil was larger

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From the Neurological Service and the Pathological Laboratory, Beth Israel Hospital.

Presented in abstract before the Sixtieth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 5, 1934.

than the left; both pupils reacted sluggishly to light, and the right eye converged poorly. Posterior rhinoscopy revealed no masses in the vault of the nasopharynx. The visual fields showed general constriction. The specific gravity of the urine varied from 1.001 to 1.004, and the total output fluctuated between 1,500 and 6,700 cc.; the fluid intake varied from 1,200 to 6,000 cc. Only once during his entire stay in the hospital did the patient exhibit any frank meningeal signs and that was during the first few weeks. He then showed a Kernig sign, but no striking rigidity of the neck.

Lumbar puncture revealed the presence of xanthochromic fluid containing 3,100 cells, mostly lymphocytes; the total protein content was 400 mg., and the sugar content was 20 mg., per hundred cubic centimeters. The Wassermann and the colloidal gold reaction were negative. A pellicle formed on standing. No tubercle bacilli were found on either smear or culture. The intrathecal pressure was normal except on one occasion when the reading was 250 mm. of water.

Diagnosis.—On the basis of the history and the findings a preliminary diagnosis of an old tumor of the pituitary gland with superimposed polyneuritis was made. However, roentgenograms failed to show any involvement of the sella. Because of the xanthochromia, the pleocytosis in the spinal fluid, the presence of a lesion of the third nerve on the right side and the normal roentgenographic appearance of the sella, the possibility of a ruptured or a leaking suprasellar cyst was considered.

The neuritis, which at first was not accompanied by pronounced sensory disturbances, was thought to be due to the chemical powder used in the hat-finishing industry, as it has been maintained that this powder contains some lead. There was, however, no lead line on the gums, or basophilic stippling of the red blood cells, and roentgen examination of the long bones failed to show the changes which are associated with chronic lead poisoning. Subsequent investigations also failed to reveal the presence of lead in the urine or in the powder used by the patient.

Course.—Shortly after admission there developed a clouding of the mentality, a complete palsy of the third nerve on the right side, progressive muscular weakness and a diminution in the senses of touch and pain over the feet and hands. A week later there was quadriparesis, the left upper extremity being the least involved. All abdominal reflexes except the left lower reflex were absent. The sensory disturbances (involving all forms of sensation) assumed the form of a stocking extending up to the knee on the right side and up to the hip on on the left. The deep reflexes later disappeared from the upper extremities as well. There was further impairment of the ocular movements, and evidences of a lesion of the third nerve on the left side made their appearance. A second lumbar puncture showed blood in all the test tubes and in the fluid obtained from two different interspaces. No tumor cells or cholesterol crystals were found in the spinal fluid. Later, hyperkeratosis of the hands was noted, but scrapings obtained from the palms did not show any evidence of lead, arsenic, mercury or antimony.

During the patient's stay at the hospital, there developed, in addition to euphoria, which had been present on admission, symptoms of an active psychosis which persisted throughout his stay. At times he was completely disoriented; at others, euphoric and facetious. The polyneuritic phenomena and ophthalmoplegia persisted.

Later examinations of the spinal fluid showed a decrease in the number of cells to 270 and 120, respectively, but the protein content remained high and

the sugar content, low. Inoculation of the brain in guinea-pigs and rabbits revealed no abnormality.

Because of the persistent radicular pain, the high protein content and the xanthochromia of the spinal fluid, the possibility of sarcomatosis of the meninges was considered, but repeated examination of the spinal fluid failed to show the presence of tumor cells. The coagulum which formed during centrifugation con-

Fig. 1.—The gross appearance of the spinal cord with much thickened spinal ganglia. The occasional thickenings of the spinal dura mater cannot be recognized in this photograph.

tained many polymorphonuclear leukocytes, some small lymphocyte-like cells and some larger round and oval mononuclear elements.[1] Encephalography revealed enlargement of the ventricular system but no evidence of displacement of or

1. Cairns and Russell (Brain **54**:417, 1931) stated that the presence in the spinal fluid of mononuclear cells other than lymphocytes should always arouse suspicion of the presence of a tumor.

encroachment on the ventricles. The surface markings were increased. The encephalogram was interpreted as indicating widespread degenerative disease of the brain and probably a diffuse lesion of the central nervous system.

Roentgen examination showed that the sella turcica was not enlarged. The clinoid processes were neither eroded nor displaced. No abnormality was revealed in the spine. Finally, respiratory difficulties, fever and cyanosis developed, and the patient died on March 27, 1933.

The clinical diagnosis was diffuse infection of the central nervous system, probably encephalomyeloradiculitis, with terminal bronchopneumonia.

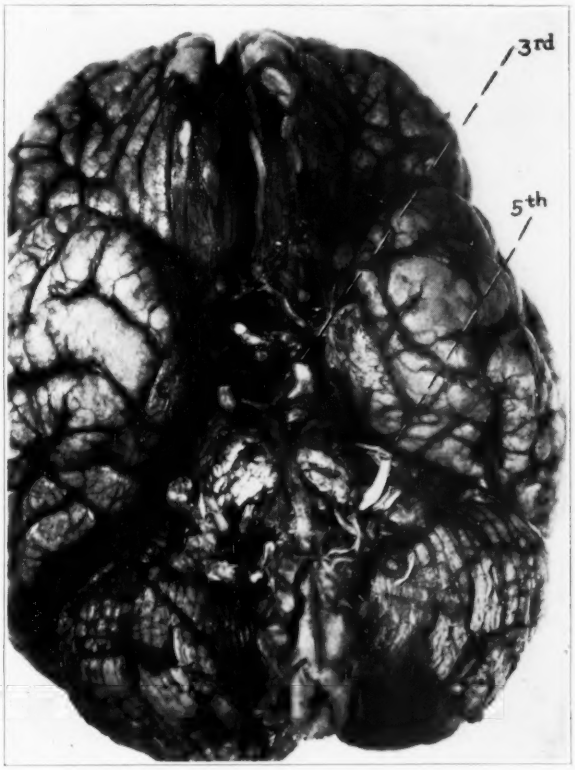

Fig. 2.—Gross appearance of the base of the brain. No tumor is seen. The third and fifth nerves (severed ends are indicated) are greatly thickened. Note the thin right optic nerve.

Gross Postmortem Examination.—The organs showed nothing that indicated that there had been any severe, long-standing disease except a decubital ulcer in the esophagus opposite the cricoid cartilage. The body was somewhat emaciated, but the lymphatic apparatus of the pharynx and of the intestine was not atrophic. Examination of the organs of the chest and abdomen revealed no abnormality.

The scalp and the skull were normal. Examination of the dura mater, its sinuses, the base of the skull, the middle ears and the hypophysis revealed nothing of importance. The large and small vessels on the surface of the brain were

injected. There was a slight conus of pressure. The soft meninges of the brain, except for hyperemia, showed nothing unusual. The basal arteries were thin-walled.

The only striking change was in the cranial nerves. The oculomotor, trigeminus and facial nerves were much thicker than normal. The thickening of the oculomotor nerves was the more conspicuous since the optic nerves and the optic chiasma were unusually thin. The olfactory nerves were normal. The other cranial nerves were less thickened. There was not much difference between the thickening of the cranial nerves of the two sides.

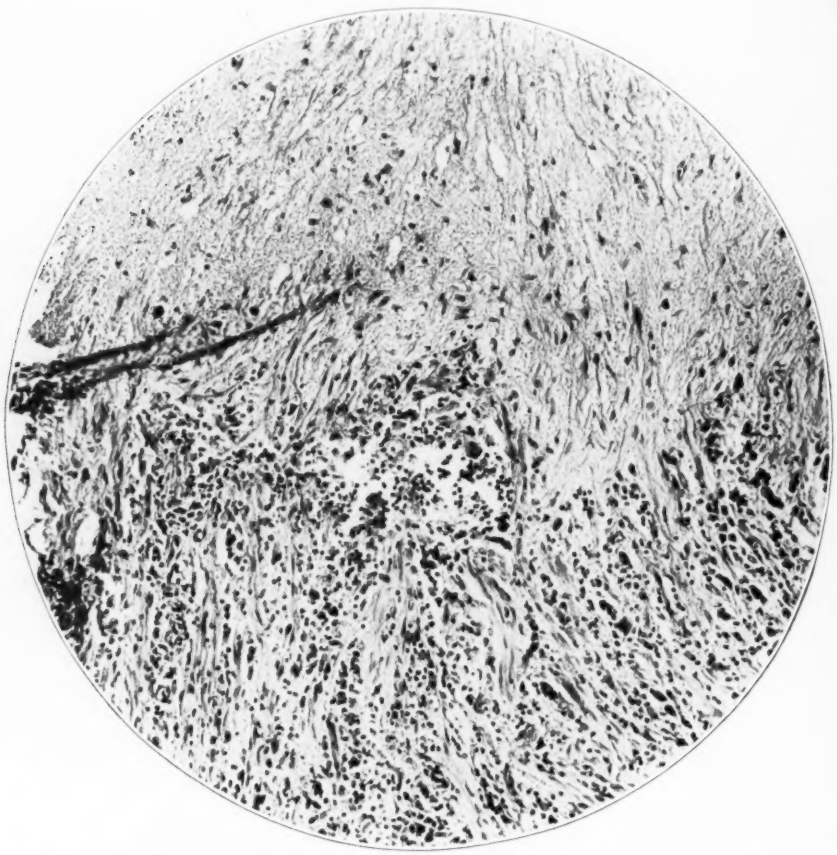

Fig. 3.—Photomicrograph of a section made at the origin of a spinal accessory nerve. The nerve is densely infiltrated; the tissue of the medulla is intact.

The spinal dura mater appeared normal outwardly. On its inner surface, in the lumbar region, occasional flat, pale gray elevations were found, the largest being about 1 cm. in diameter. The soft meninges of the spinal cord appeared in spots a little more opaque than normal, without showing any definite thickening. A most striking change was present in the spinal ganglia, which were firm and at least three times as large as normal. The cut surfaces were grayish-white and without markings. The filaments of the cauda equina were much thicker than normal; in addition to their general thickening, spindle-shaped, circumscribed swellings were found, notably in the lower portions. Some of the filaments adhered

to the dura mater, and most of them stuck together much more closely than normally. The conus itself did not appear considerably thickened. A few cross-sections of the spinal cord revealed nothing unusual.

A diagnosis could not be made from the gross appearance of the brain or spinal cord.

Microscopic Postmortem Examination.—After fixation in a dilute solution of formaldehyde, U. S. P., the brain was sliced. No circumscribed lesions were found

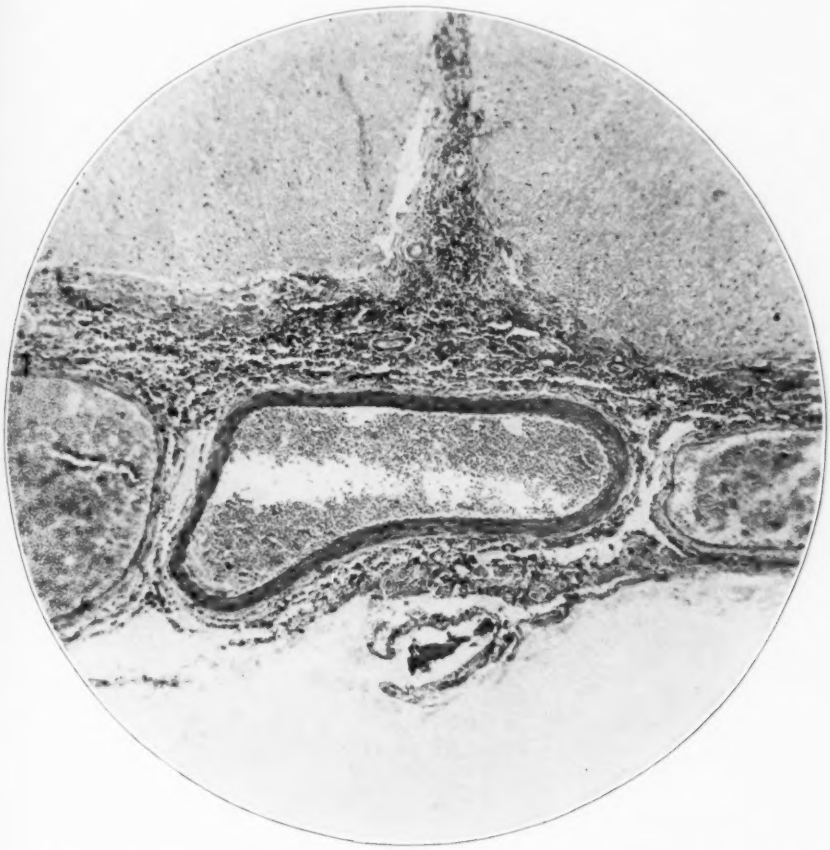

Fig. 4.—Photomicrograph of a section of tumor of the soft meninges of the spinal cord which is invading the corona. The tissue of the spinal cord proper is intact. The dark, irregular formation in the lower portion of the picture is calcific material.

anywhere and the tissue appeared normal throughout. All the ventricles were widened. The venae cerebri internae and the vena cerebri magna (Galeni) were thrombosed and surrounded by indefinite layers of a tissue the consistency of which could not be judged because it had not been examined before fixation. No special attention was paid to these findings or to the pineal gland on the first examination of the fixed brain.

The microscopic study of the first slides of a spinal ganglion and of the oculomotor nerve also did not lead to a definite diagnosis. There was a diffuse infiltration of the nerves, ganglia and meninges. Large and medium-sized cells without any stroma occupied the tissue spaces and widely supplanted the tissues. The picture did not resemble that of any familiar tumor or inflammation. A study of the literature on diffuse sarcomatosis of the meninges yielded no similar picture. An attempt was therefore made to compare this histologic picture with

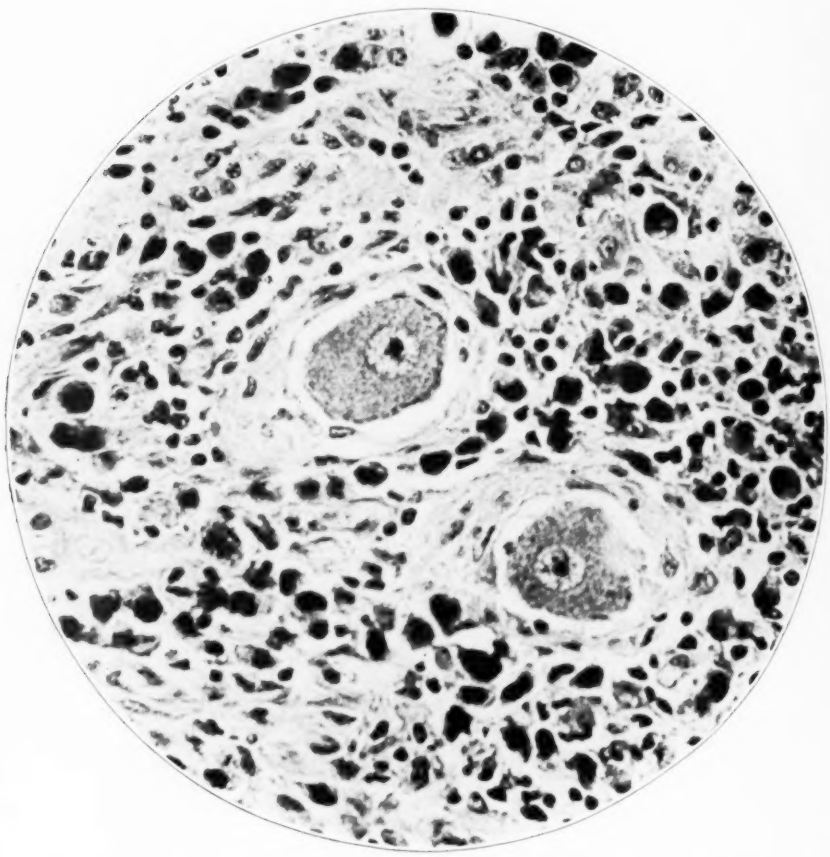

Fig. 5.—High power photomicrograph of a section showing ganglion cells in a spinal ganglion surrounded by tumor cells. In this section the large tumor cells predominate.

that of the normal cells of some organ, and the striking similarity of the pathologic cells to the normal cells of the pineal gland then became evident. The gross study of the specimen was then resumed, particularly of the region of the pineal gland. The habenulae were intact and attached to them was an irregularly round nodule the size of a large pea which seemed to be the pineal gland. Small, stone-hard masses could be felt in it. Microscopically this nodule was found to be composed of the same types of cells that were found in the other tumor masses.

There were a few areas in which the cells were arranged in a network of broad strands of dense connective tissue, such as are found in the normal pineal gland of the adult.

Many different portions of the brain, cranial nerves, spinal cord, spinal ganglia and meninges were found to contain the same kind of tumor tissue. The neoplastic infiltration was diffuse throughout the meninges, nerves and ganglia, but stopped abruptly at the central nerve tissue proper. The brain and the spinal cord con-

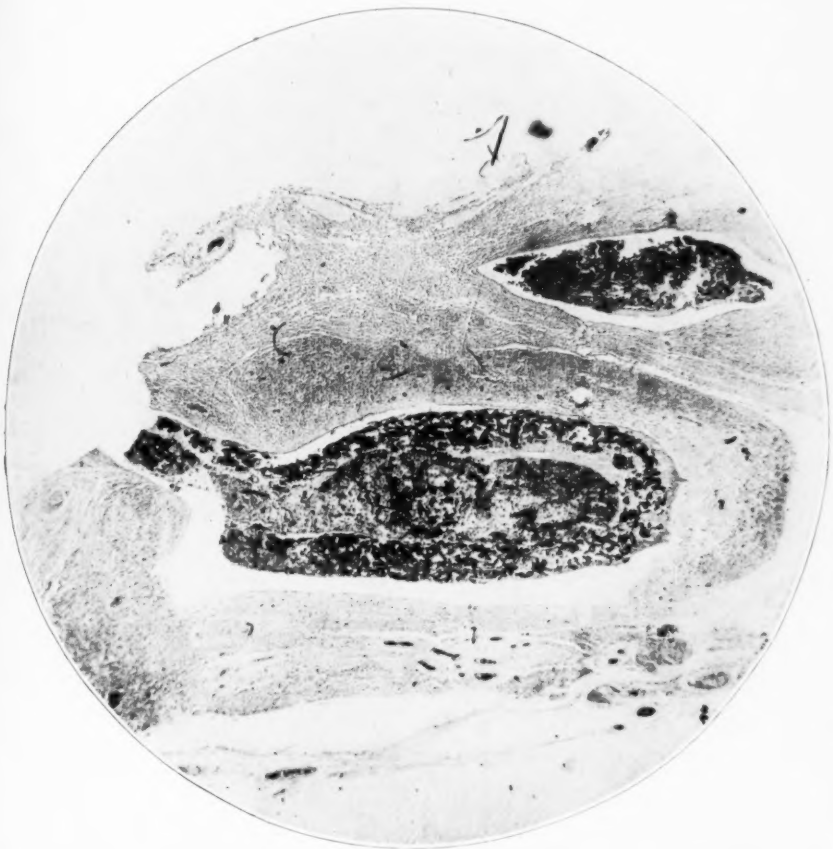

Fig. 6.—Photomicrograph of a section of the thrombosed vena cerebri magna surrounded by tumor cells.

tained tumor tissue only in the vicinity of the blood vessels which enter these organs. The infiltration was densest in the nerves and ganglia, and less dense in the meningeal lesion. Only the peripheral portions of the brain and the spinal cord had tumor tissue in the perivascular spaces. Aside from different portions of the cortex, the examination included the cerebellum, hippocampus, basal ganglia, pons, septum pellucidum, corpora quadrigemina, tuber cinereum and infundibular region. No more tumor tissue was found in the infundibular region than in other portions of the brain. The olfactory and optic nerves did not contain tumor

tissue, but the meninges in their vicinity were densely infiltrated. The filaments of the cauda equina also were densely infiltrated. Although the cerebral dura mater contained no tumor tissue, thick tumor masses were found on the spinal dura mater corresponding to the whitish areas which were visible to the naked eye. The anterior and posterior roots were densely infiltrated. In the cranial nerves the nerve tissue was destroyed in varying degrees. In the oculomotor nerves hardly any nerve tissue was found. In the spinal ganglia the ganglion cells

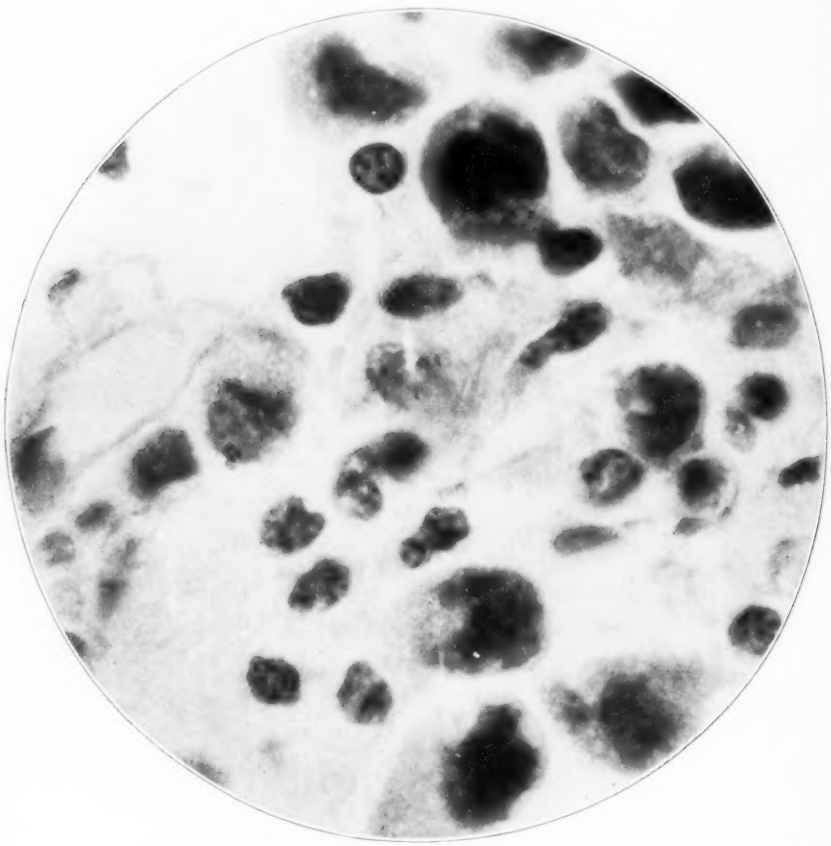

Fig. 7.—Near the center of the photomicrograph of a section of the pinealocytoma the irregular shape of the small tumor cells and of their nuclei can be recognized. They do not have the morphologic appearance of lymphocytes. One of the large cells in the upper portion of the field has a bilobate nuclear inclusion.

appeared well preserved, while the other tissue elements were widely destroyed. Unfortunately, the gasserian ganglion was not examined. The root of the facial nerve was densely infiltrated by tumor cells.

The aforementioned masses which surrounded the thrombosed vena magna and its tributaries consisted of the same tumor tissue. The thrombus in this vein consisted mainly of platelets and leukocytes. The habenulae themselves did not

contain tumor tissue. The small mass which was found in the place of the pineal gland contained acervulus next to the attachment, while the more distal portions consisted of tumor tissue and of areas which represented remnants of the normal pineal gland. The choroid plexus of the lateral ventricles did not contain tumor tissue. There was little tumor tissue in the choroid plexus of the third ventricle, but the plexus in the fourth ventricle was densely infiltrated. Tumor tissue covered fragments of the dura mater which were attached to the hypophysis.

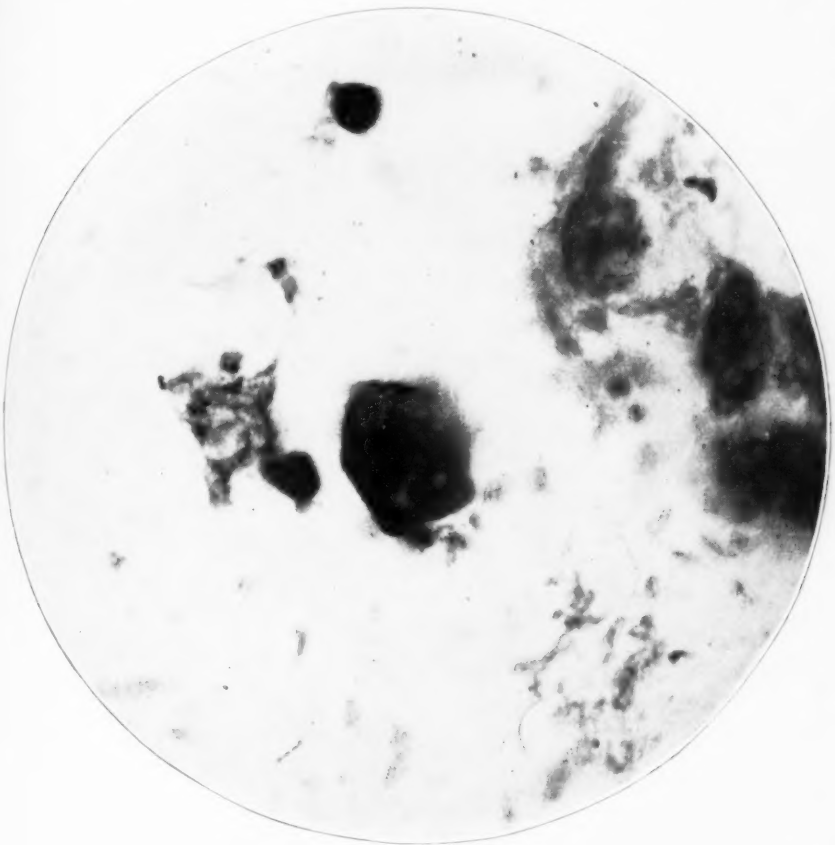

Fig. 8.—Photomicrograph of a section of the pinealocytoma showing a large tumor cell under an oil immersion lens. A large, larkly staining nuclear inclusion is seen within the vesicular nucleus. Directly outside the nucleus a vacuole is situated in the cytoplasm.

Near the attachment of the hypophyseal stalk a small area of the anterior lobe was invaded by tumor tissue. The posterior lobe of the hypophysis was unusually small and dense, and seemed to contain more nuclei and blood vessels than normally. Otherwise the hypophysis was not remarkable.

Nothing abnormal was found in a section from the femoral nerve.

Microscopic Appearance of the Pineal Tumor.—Many staining methods were used, but the microscopic details of the tumor of the pineal gland were well brought out with hematoxylin and eosin in thin paraffin sections, and the diagnosis was made from these sections.

As previously mentioned, the affected tissues were diffusely infiltrated with epithelium-like cells not supported by stroma. We therefore could not demonstrate the architecture of the tumor and must confine ourselves to describing its

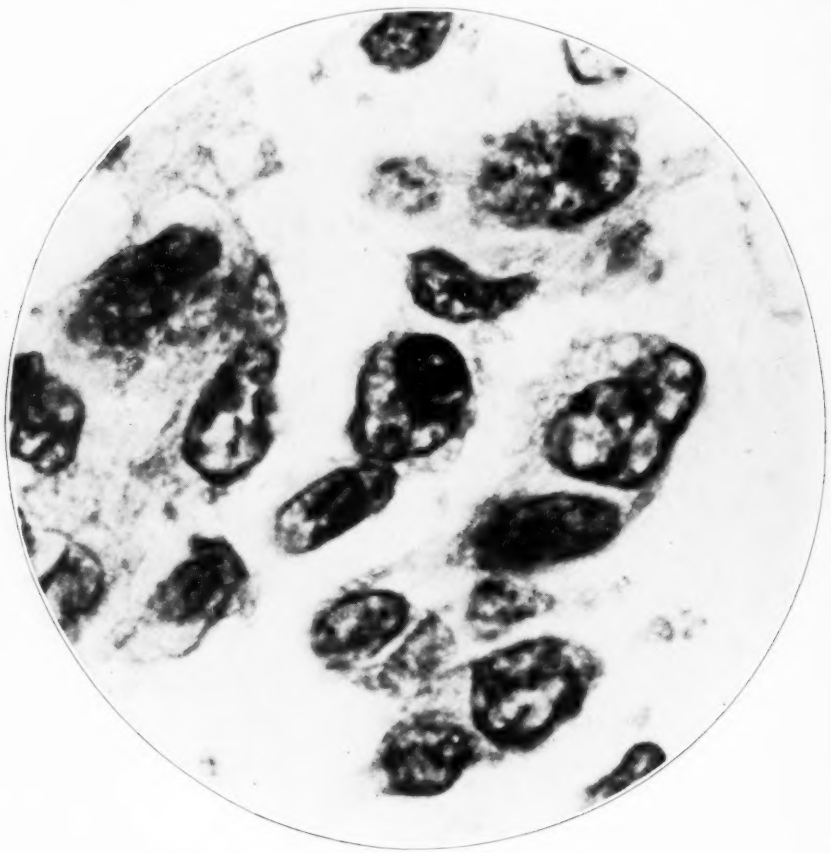

Fig. 9.—Photomicrograph of a section of control specimen, showing a cell from the ependyma of the recessus pinealis of a normal person. The cell is practically identical in appearance with the tumor cell described in figure 8.

cells from the beginning. Of the two types of cells which composed the tumor, the larger ones were more characteristic. A superficial examination of these large cells might lead to an erroneous conclusion; many of them had a faint protoplasm which could easily be overlooked, a large vesicular nucleus which might be taken for the cytoplasm and a conspicuous nuclear inclusion which would in that case be mistaken for the nucleus. Figures 8, 9 and 10 illustrate the true interpretation of these cells. The protoplasm formed a narrow or wide

margin around the large nucleus, was loose and in general stained poorly. No protoplasmic structures were seen with the ordinary methods. The outlines of the protoplasm were mostly indistinct. Sometimes vacuoles were found, notably near the nucleus. The nucleus, which, as mentioned, was large and vesicular, had a distinct outer layer, probably corresponding to a nuclear membrane. There was only a little chomatin, and it was distributed in small, irregular bits. The really characteristic feature of the large cells was the nuclear inclusion, a deeply

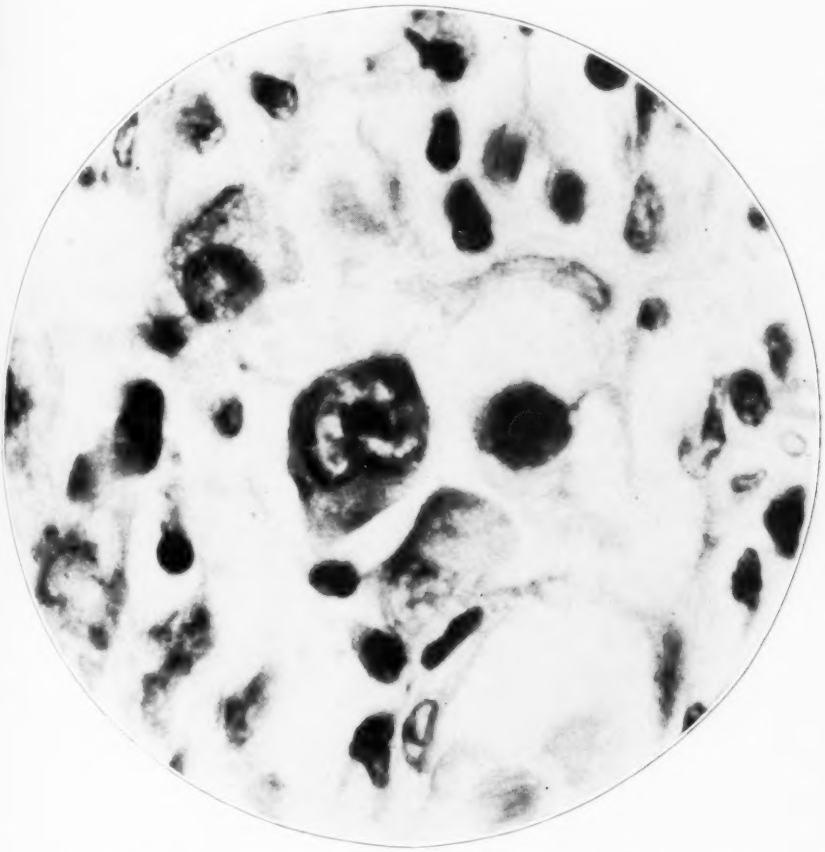

Fig. 10.—Photomicrograph showing another large tumor cell. Its cytoplasm is distinct and tapers off as if forming a processus. The nuclear inclusion is situated in a fold of the irregularly shaped nucleus.

staining, irregularly rounded mass, usually one-fourth the size of the nucleus but sometimes considerably larger, situated near the nuclear membrane. The nucleus often was irregularly shaped with complicated folding of the membrane, and sometimes the nuclear inclusion seemed to be situated under the deepest point of the fold. Mitotic figures were seen not infrequently. Some of the cell forms might have been interpreted as evidence of amitotic cell division.

The small cells had a superficial similarity to lymphocytes, but they were not round; their nuclei likewise were not round, some of them being dumb-bell-shaped or bean-shaped (fig. 7). The chromatin was not arranged in characteristic fashion. No division of the small cells was observed.

The two kinds of cells were intermingled without apparent order, but in most slides the large cells were more numerous. Neither the distance from the primary tumor nor that from the meningeal surface seemed to influence the prevalence

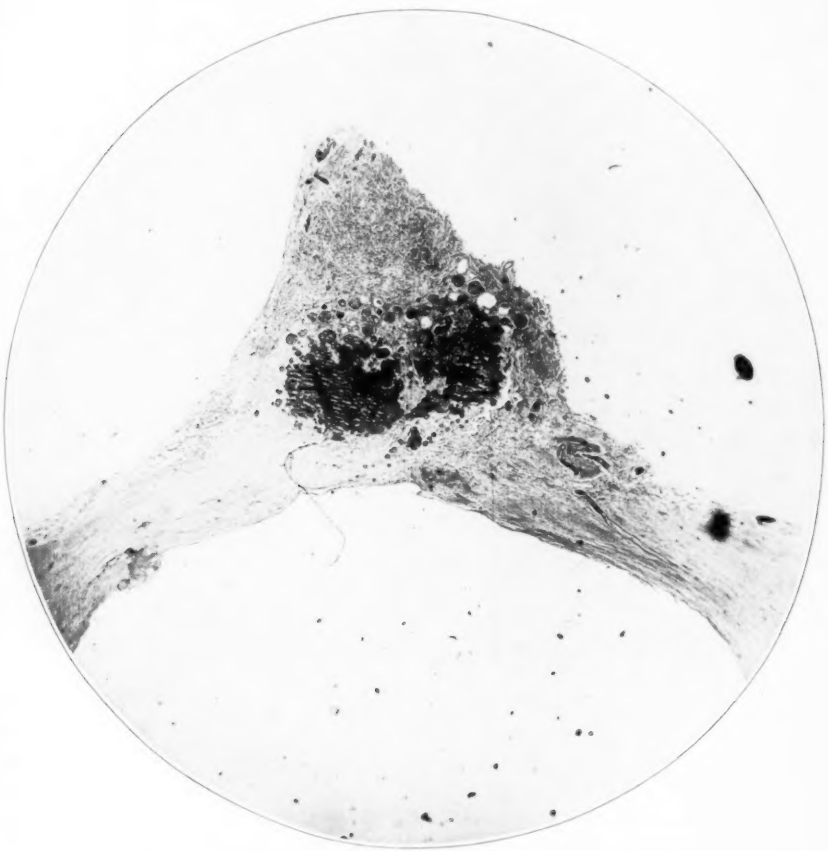

Fig. 11.—Low power photomicrograph of a section of the tumor from the pineal region, showing the presence of acervulus.

of one or the other type of cell. The "mosaic structure" (Globus and Silbert),[2] which is caused by narrow, more closely packed strands of small cells encircling clear areas of large cells, was not seen in our case.

Aside from the two characteristic types of cell there were many cells which did not exhibit definite features, although they could be included in one of the

2. Globus, J. H., and Silbert, S.: Pinealomas, Arch. Neurol. & Psychiat. **25**:937 (May) 1931.

two categories according to size. No attempt was made to define the nature of every cell. In the case of many cells it was doubtful whether they belonged to the tumor or to the invaded tissue (neuroglia, for instance). The large foreign body giant cells which were found in the region of the primary tumor near the vena magna obviously were not tumor cells. One of them contained a fragment of acervulus. No granular elements were found.

The microscopic appearance was characteristic of a true pinealoma, i. e., a tumor composed of the specific cells of the pineal gland. As our observation adds nothing new to this rare but highly characteristic histologic entity, we abstain from giving the complete histologic details and mention only a few salient points.

The most unusual feature of the microscopic picture was, in our opinion, the complete absence of stroma in a tumor which had nothing in common with a sarcoma. Globus and Silbert have considered the small cells to be the stroma. They observed a connection between these cells and the formation of fibroblasts. But even if this is so, there still remains the question of how a tumor consisting of highly differentiated, nonmesoblastic cells could grow without supporting fibers. Since the tumor cells did not form continuous sheets, this mode of growth appears all the more unusual.

The much debated question as to the character of the large pineal cell will not be entered on here. We applied special stains without gaining much knowledge concerning it. While we were unable to demonstrate cell processes by the silver carbonate method of Hortega in our tumor or in normal pineal glands, we found it easy to stain club-shaped and other prolongations of the tumor cells with phosphotungstic acid hematoxylin (Davidoff and Ferraro[3]). We think, in full accord with Berblinger,[4] that the appearance of the pineal cells is sufficiently characteristic, even in the absence of demonstrable prolongations of the cells.

HISTORICAL DATA

From the literature on pineal tumors it is difficult to group the cases in a satisfactory fashion. This is because, especially in older reports, the microscopic descriptions are not always sufficiently detailed to permit recognition of the important cytologic features. We shall mention only cases which can be recognized as belonging histologically to the same type as ours, namely, the true pinealocytoma. In addition to the cases mentioned by Berblinger, the following instances have been included:

1. Of the cases of pineal tumor reported by Horrax and Bailey[5a] in 1925 cases 4, 7, 8 and 10 belong to our group, perhaps also cases 9 and 12.

2. From the photomicrograph given it is evident that the pineal tumor reported by Davidoff and Ferraro in 1929 was a pinealocytoma.

3. Globus and Silbert's paper[2] (1931) contained reports of 6 cases in which according to the pictures given, the growths were definite pinealocytomas.

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3. Davidoff, L. M., and Ferraro, A.: Intracranial Tumors Among Mental Hospital Patients, Am. J. Psychiat. **8**:599, 1929.

4. Berblinger, W.: (*a*) Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:741, 1925; (*b*) Ergebn. d. ges. Med. **14**:245, 1930; (*c*) in Hencke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 731.

5. Horrax, G., and Bailey, P.: (*a*) Tumors of the Pineal Body, Arch. Neurol. & Psychiat. **13**:423 (April) 1925; (*b*) Pineal Pathology: Further Studies, ibid. **19**:394 (March) 1928.

Thus, these tumors seem to be much less rare than appeared nine years ago when Berblinger [4c] published his article in the handbook of pathology.

All the cases mentioned have occurred in males and in young persons. One of the patients reported on by Globus and Silbert was 37; our patient was 33, and Berblinger's was 32. All the others were under 30. In none of the cases except Berblinger's and ours did metastases occur.

COMMENT

Our case demonstrates the specific character of the histologic picture of pinealoma, or pinealocytoma, since in the absence of a conspicuous primary tumor the microscopic picture alone enabled us to make the diagnosis. Renewed gross and microscopic study of the region of the pineal gland verified the diagnosis. If further proof should be deemed necessary, it could be found in the almost complete parallelism between our case and that of Berblinger, the only important difference being the large tumor of the pineal gland found in Berblinger's case. The photographs of the gross appearance of the cauda equina in the two cases could be substituted for one another. As far as our knowledge of the literature goes, no other similar case has been reported, and we therefore present the salient features of these two cases in the form of a table.

The striking similarity between Berblinger's case and ours might be explained in two ways. One could assume that tumors of the pineal gland, by virtue of some inherent unknown factor, metastasize with the spinal fluid. The absence of similar cases among the many reports of tumors of the pineal gland, however, speaks against this assumption. Haldeman,[6] in reviewing one hundred and thirteen cases of tumor of the pineal gland, did not mention involvement of the spinal cord or of the nerves. The other possibility is that the cells of any tumor which is situated at or near the surface of a ventricle or of the subarachnoid space may be distributed by the spinal fluid. This explanation seems to us to be the more probable. Tumors (so-called carcinomas) of the choroid plexus do metastasize into the subarachnoid spaces. Kono [7] reported such a case in which he found tumor cells in the spinal fluid after death. The primary tumor in his case was a carcinoma of the choroid plexus. Hall and Fentress [8] described a case of papilloma of the choroid plexus which, in the distribution of the secondary deposits, closely resembled our case. They found diffusely opaque and thickened leptomeninges, notably in the lumbar and cerebellar regions. A tumor the size of an olive was attached to the cauda equina. The ventricles of the brain, however, appeared normal to the naked eye, and the primary tumor in the choroid plexus was found only on microscopic examination.

The conditions under which the seeding process takes place are unknown. Berblinger's case and ours, the only cases of pineal tumor in which seeding has been observed, have one thing in common—the extreme paucity of stroma; but this does not apply to tumors of the choroid plexus, which may also metastasize in this fashion.

In cases of cerebral glioma, also, proximity of the tumor to the ventricular system or to the basal cistern is most important in promoting metastases to the spinal meninges. Cairns and Russell [1] found such metastases in eight of twenty-two cases of glioma and in three other instances of intracranial tumor. They

6. Haldeman, K. O.: Tumors of the Pineal Gland, Arch. Neurol. & Psychiat. **18**:724 (Nov.) 1927.

7. Kono, N.: Frankfurt. Ztschr. f. Path. **30**:92, 1924.

8. Hall, G. W., and Fentress, T. L.: J. Neurol. & Psychopath. **14**:108, 1933.

expressed the belief that spinal meningeal metastases must be more frequent than has hitherto been assumed. They asked for examination of the spinal cord in every case of brain tumor which comes to autopsy.

We have studied the literature on diffuse sarcomatosis of the meninges in the hope of finding an instance which might have a bearing on our case and which might have been interpreted differently, but have found nothing. Spinal ganglia

Comparison of the Case of Pinealocytoma Reported by Berblinger and the Case Reported by Us.

Berblinger's Case	Our Case
Man, aged 32	Man, aged 33
Clinically diagnosed as meningomyeloencephalitis or brain tumor	Clinically diagnosed as encephalomyeloradiculitis
Loss of sexual power; no other endocrine disturbance	Loss of sexual power; transient diabetes insipidus
Tumor 3 by 2.6 cm. in region of corpora quadrigemina; pineal gland not found	Pineal gland small; no gross tumor in region of pineal gland
Vena magna and its tributaries thrombosed	Venae internae and vena magna thrombosed
Cranial nerves infiltrated; left more than right	Cranial nerves infiltrated; left slightly more than right
Soft meninges on convexity of brain transparent	Soft meninges of brain grossly not remarkable
Dura mater intact	Flat tumor masses on inside of dura mater spinalis
Soft meninges in lumbar region opaque	Spinal soft meninges slightly opaque
Spinal ganglia not mentioned	Spinal ganglia large and firm
Nerves of cauda equina glued together by whitish masses; many spindle-shaped swellings	Filaments of cauda diffusely thickened; circumscribed spindle-shaped thickenings
Blood vessels not invaded	Blood vessels not invaded
Some noninfiltrated zones in spinal meninges	Continuous infiltration of spinal meninges
Acervulus notably in anteroventral portion of tumor	Acervulus notably near habenulae
Large tumor cells more numerous	Large cells slightly more numerous
Indication of amitotic cell division	Mitotic figures numerous; probably amitotic cell division
Nuclear inclusions in the primary tumor only	Nuclear inclusions throughout metastases
Hypophysis normal	Small portion of anterior lobe invaded by tumor; changes in posterior lobe possibly due to roentgen therapy
Posteriorly in lumbar region the tumor encroaches on the substance of the spinal cord	Tissue of brain and spinal cord not invaded

and nerves do not seem to be invaded by diffuse sarcoma. According to Ewing the diffuse invasion of the soft meninges is not peculiar to any specific form of sarcoma. Cases in which there is no localized tumor stand out clinically as representing a disease *sui generis*, notably in young persons.

We thought of examining our tumor biologically with the Gudernatsch tadpole test. We knew, however, from previous work, the great variation in the reaction of tumor-fed tadpoles. On the other hand, there is no generally accepted reaction for tadpoles which have been fed pineal gland (Gudernatsch, Romeis, Dana and Berkeley, McCord and Allen); hence, we did not consider it particularly promising to attempt tests on tadpoles.

It is not our purpose in this report to discuss either the possible endocrine character of the pineal gland or its anatomic classification, especially since our patient did not manifest any endocrine disturbances similar to those that have been ascribed to disease of the pineal gland and since no striking change in an endocrine organ was found at autopsy. The slight changes that existed in the posterior lobe of the hypophysis may have been caused by roentgen treatment. The reason for the preponderance of cases among young men and the entirely inconstant relation to precocious puberty are questions we cannot answer.

The infundibular symptoms, which appeared first, disappeared in large part. Clinically, however, the patient retained a somewhat hypogenital hypophyseal habitus. Years later, in the months before death, he again showed polydipsia and polyuria. The question arises as to whether this late diabetes insipidus had anything to do with the tumor of the pineal gland. Von Gierke[9] reported the case of a woman aged 72 who suffered from diabetes insipidus without exhibiting any lesion in the hypophysis or the midbrain; but he found a metastasis from a mammary carcinoma in the pineal gland. Von Gierke has discussed the possibility of a relationship between metastasis in the pineal gland and diabetes insipidus. Similar cases have been reported by Massot, von Hoesslin and van den Bergh, the tumors having been a carcinoma in one case, a sarcoma in another and an embryoma in a third. We are unable to affirm or to deny a relationship between a lesion of the pineal gland and diabetes insipidus, but we wish to point out this coincidence.

The internal hydrocephalus which was present in our patient remains to be explained, since the region of the aqueduct was normal. In all probability the low grade hydrocephalus was principally of the nonresorptive type (hydrocephalus aresorptorius of Foerster). The soft meninges and the roots of the cerebral and spinal nerves were densely infiltrated by tumor cells. Thus there was interference with the absorption of spinal fluid, which normally takes place in the perineural spaces. It may be mentioned in this connection that foreign material introduced into the spinal canal has been found in the perineural lymph spaces (Kono). In accordance with Hassin,[10] therefore, we believe that the obliteration of perineural spaces can be a factor in the causation of hydrocephalus. Our case may be considered as suggestive proof of this contention, but Berblinger's case does not support it because his patient had a large intracranial tumor with probable blocking of the aqueduct.

The question of nomenclature requires discussion. A tumor with a well defined histologic picture deserves a name of its own. Berblinger, taking the epithelial nature of the cells of the pineal gland for granted, spoke of pineal carcinoma and

9. von Gierke, E.: Verhandl. d. deutsch. path. Gesellsch. **17**:200, 1914.

10. Hassin, G. B.: Hydrocephalus, Arch. Neurol. & Psychiat. **24**:1164 (Dec.) 1930; Hydrocephalus, ibid. **27**:406 (Feb.) 1932.

pineal adenoma. Uemura [11] stated that the absence of true glandular structures does not prevent one from designating tumors of the anterior lobe of the hypophysis as adenomas. The same principle applies to the pineal gland, provided one considers its cells epithelial. Berblinger made use of the term pinealoma (Krabbe) for both the adenoma and the carcinoma. The morphologic identity of the large tumor cell and the normal ependymal cell of the recessus pinealis speaks in favor of the epithelial nature of the large tumor cell (figs. 8 and 9). Berblinger wrote: "The pineal gland according to its anlage is of purely epithelial origin, and the cells which form its parenchyma are all derivatives of the neural ectoderm." Comparative anatomy also indicates the epithelial character of the pineal gland (Tilney [12]). In view of the prevailing disagreement concerning the nature of the pineal gland, it seems desirable to have a name which designates the origin of the tumor from the pineal cell without making a statement as to the nature of the pineal parenchyma. The term pinealoma is widely used. Cushing,[13] on the other hand, preferred to call all tumors of the region of the pineal gland pinealomas without having the term "connote any particular type of tumor."

It is against the rules of pathologic nomenclature to designate a tumor by means of the name of an organ, the merits of this rule being clearly shown by the fate of the term hypernephroma. Pending decision on the developmental anatomy of the pineal gland, however, it might be agreed to name the specific tumor after the organ. Of all existing names, pinealcytoma seems least objectionable to us.[14] From the standpoint of the philologist all these names which begin with pineal are monstrosities because they are derived from an adjective, but the noun conarium is so little used that it seems better to sacrifice linguistic propriety to intelligibility and to use the term pinealocytoma.

SUMMARY

A tumor is described the cells of which were characteristic of the pineal gland. It metastasized diffusely into the soft meninges, spinal ganglia and nerves down to the cauda equina. The primary tumor remained small and did not give rise to local symptoms; furthermore, it did not strikingly alter the morphologic picture of the endocrine organs. The diagnosis of pinealocytoma was made from the microscopic appearance of the metastases.

11. Uemura, S.: Frankfurt. Ztschr. f. Path. **20**:452, 1917.

12. Tilney, F., and Cowdry, E. V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1928, vol. 1, p. 502; Am. Anat. Mem. **9**:7 (Feb.) 1919.

13. Cushing, H.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 63.

14. Berblinger,[1a] p. 749.

Abstracts from Current Literature

THE CELLULAR STRUCTURE OF THE THALAMUS IN MAMMALS AND IN MAN: A DESCRIPTIVE AND COMPARATIVE ANATOMIC STUDY. ERNST GRÜNTHAL, J. f. Psychol. u. Neurol. **46**:41, 1934.

As one ascends the mammalian scale, the zona incerta, which Grünthal includes in the thalamus, becomes relatively smaller. It is largest in the mouse and of considerable size in the macacus; it is strikingly small in the chimpanzee. In the lower mammals it extends posteriorly almost to the end of the thalamus. In primates it disappears with the appearance of the external geniculate bodies; in the lower mammals this occurs much later in the development of the brain. In the dog the zona incerta still extends to the most posterior portion of the thalamus, whereas in the macacus it terminates at the level of the pulvinar.

The group of nuclei situated laterally to the zona incerta in all series of animals occupies from one third to one half of the entire size of the thalamus. Close examination of this group reveals three definite subgroups, each of which has its own peculiarities. Grünthal designates the nuclei in the most ventral portion of the thalamus as the prethalamic nuclei, which are subdivided into two parts in the lowest mammals (Marsupialia, mice); in the dog they merge with the nucleus dorsalis, and in primates they are entirely absent.

Another ventrolateral group (nucleus lateralis anterior) is found in all mammals in almost the same differentiation. In Marsupialia and in mice it is divided in three parts and in the remaining mammals in two. In the former, the nucleus lateralis anterior A is larger than in the higher mammals, and it extends more caudad; correspondingly, the zona incerta appears in these animals much later. In these animals there is also found the nucleus lateralis anterior C, originating from the nucleus lateralis anterior A.

The nucleus lateralis anterior B is unusually well developed in Marsupialia and is situated dorsally to the nucleus lateralis principalis (the principal lateral nucleus), extending down to the end of the thalamus. The structure of this nucleus is uniform throughout its entire extent. In contrast to its position in Marsupialia, the nucleus lateralis B in the higher mammals is situated more ventrally; in primates it is considerably smaller, so that the lateral principal nucleus occupies the entire field. This nucleus in the mouse consists of four subdivisions; in mammals ranging from the dog to the chimpanzee, it consists of seven subdivisions, and in man, of eight. In man, the eighth nucleus lateralis principalis is considerably smaller than in the chimpanzee while, on the other hand, the seventh nucleus lateralis principalis is much larger and constitutes a structure which is specific for man.

In the outer margin of the caudal portions of the thalamus there is found in man and in primates, in the region of the stratum reticulum Arnoldi, a strip of cells which does not represent a special structure but consists of cells originating from the laterally situated nuclei.

The dorsal nuclear group is found on the dorsal ventricular margin lateral to the taenia thalami and is subdivided by Grünthal into an anterior and a posterior portion. Le Gros Clark distinguished in Insectivora three parts in the nucleus anterior: (1) the nucleus anterodorsalis, (2) the nucleus anteroventralis and (3) the nucleus anteromedialis. Clark found that the nucleus anterodorsalis becomes smaller as one ascends the mammalian scale and has almost disappeared in man.

An examination of the posterior dorsal group reveals first the nucleus dorsalis posterior A. Some authors include this nucleus in the lateral group. Grünthal, however, believes that this is a separate nucleus, even though it always abuts on the lateral nucleus. In Marsupialia this nucleus is situated dorsolaterally to the nucleus lateralis; in the mouse and the dog it is entirely dorsal and in the macacus,

more mesial. In primates it is found caudad to the nucleus anterior, and in lower mammals it is always lateral to it. The nucleus dorsalis posterior A is considerably larger in lower than in higher mammals. Furthermore, the posterior dorsal group contains the nucleus dorsalis posterior B situated mesial to the nucleus dorsalis posterior A. The former is usually a small nucleus, but it is much more extensive in Marsupialia and in the dog. Its nerve cells are more closely packed than in the nucleus dorsalis posterior A. It is not found in man, and although very small in the chimpanzee it can still be recognized.

Mesial to the taenia thalami is situated the nucleus internus, frequently designated as the nucleus medialis. This nucleus is one of the constant nuclei of the thalamus and consists, in the entire mammalian series, of two poorly differentiated structures. The line of demarcation between these two structures varies in different animals. In Marsupialia it is almost perpendicular; as one ascends the mammalian scale it rotates mesially, whereas in man it makes an angle of almost 90 degrees. These variations in the position of the line of demarcation correspond to the change in position of the entire thalamus in the different animals. In all animals the lateral portion of the nucleus internus consists of widely scattered larger cells, whereas its mesial portion is made up of smaller closely packed elements. It is noteworthy that the nucleus internus in Marsupialia can be found throughout the entire thalamus; in the remaining mammals it does not appear till the termination of the nucleus anterior and disappears in the region of Meynert's bundle.

Lying closely lateral and ventral to the nucleus internus and always connected with it is the nucleus circularis, which is traversed in some places by fiber tracts derived from the internal white substance of the thalamus. In primates, however, this does not occur in all places. The nerve cells of this nucleus appear characteristically well stained. The nucleus is quite extensive in Marsupialia and small in the mouse in which, owing to different types of cells, it is divided in two parts. It is of the same size in the dog and in the macacus, in which it consists of three parts, and in some places it extends to the centrum medianum Luysii. In the chimpanzee it appears anteriorly in the form of a sharply delineated area of similar structure extending laterally and ventrally; farther back it runs dorsal and ventral to the nucleus internus. Its most posterior portion flattens out and reaches the posterior part of the pulvinar at the margin of the quadrigeminal roof. In man, it surrounds anteriorly first the dorsolateral portion of the nucleus internus and further down the lateroventral portion of this structure; it is more extensive in the pulvinar in man than in the chimpanzee. Its structure is uniform.

The centrum medianum Luysii and the nucleus semilunaris (arcuatus, Flechsig) are found in these forms only in primates. In lower mammals there are found between the lateral group of nuclei and the nucleus internus various indefinite structures which correspond to the centrum medianum Luysii and the nucleus semilunaris arcuatus in primates. There is, however, no morphologic or functional similarity between them.

As far as the pulvinar is concerned, no trace of such a structure can be found in Marsupialia and in the mouse. In these mammals the caudal portion of the thalamus is covered by the roof of the mesencephalon, which also contains the nucleus pretectalis. In the dog and in primates the posterior portion of the thalamus and the roof of the mesencephalon have an entirely different appearance. The quadrigeminal region no longer covers the thalamus. In half-apes, the primitive well developed mesencephalic roof still exists in spite of the presence of definite pulvinar nuclei which naturally lie more laterally. A definite pulvinar appears for the first time in the macacus.

The parafascicular group of nuclei consists of one nucleus in Marsupialia, three in the mouse, five in the dog and two in the macacus; in the chimpanzee and in man it cannot be found. The ventral group of nuclei consists of three nuclei in Marsupialia, one in the mouse, two in the dog, four in the macacus, two in the chimpanzee and two in man. The median group consists of an anterior and a posterior group of nuclei. The anterior group is made up of three nuclei in Marsupialia, four in the mouse, three in the dog, three in the macacus, two in

the chimpanzee and one in man, whereas the posterior group consists of four nuclei in Marsupialia, seven in the mouse, seven in the dog, eleven in the macacus, nine in the chimpanzee and seven in man.

The habenular group consists of three definite nuclear structures in the entire series of mammals.

It is noteworthy that the structural differentiation of the thalamus rises as one ascends the mammalian scale only up to the lower apes. In man and the chimpanzee the number of thalamic nuclei is one fourth less than in lower mammals. It seems, therefore, that up to a certain point the nuclear content of the thalamus corresponds to the cellular richness of the cerebral cortex, but when the cortex is unusually well developed—in anthropoids and in man—the thalamus regresses to a primitive stage. This phenomenon, however, appears only late in the development of the entire brain, whereas in the hypothalamus a simplification of this originally most complex structure occurs from the very beginning of development in the entire mammalian series. The great variability in the structure of the thalamus of lower mammals depends chiefly on the existence of a later completely disappearing prethalamic and parafascicular group of nuclei as well as on the greater number of mesial nuclei.

Grünthal next discusses the specific structural features of the human thalamus, especially as compared with that of the chimpanzee. His conclusions of this part of the paper may be summarized as follows:

In man the mesial group of nuclei is much smaller than in the chimpanzee as compared with the macacus. The first nucleus ventralis, constantly found in all mammals, is absent in man. In the lateral group of nuclei, a nucleus which is considerably developed in the chimpanzee is replaced in man by a new kind of nucleus. In the pulvinar there are two nuclei found exclusively in man; as compared with the chimpanzee these two principal nuclei show great variations in size. Although the nerve cells of the thalamus in man resemble those in the chimpanzee, they are larger in size in the former and much more diffusely scattered. In comparison with the size of the entire thalamus the nucleus internus is much larger in man than in the chimpanzee. The nucleus anterior, though less extensive, is also much larger in man. The entire thalamus in man, however, is much smaller in proportion to the volume of the entire brain. KESCHNER, New York.

PROBLEMS IN THE PHYSIOLOGY OF VISUAL ACUITY. FRANCIS HEED ADLER, Arch. Ophth. **11**:6 (Jan.) 1934.

In discussing certain problems in the physiology of visual acuity, Adler, of necessity, divides his subject into a consideration of the light sense, the color sense and the form sense. Each of these is more or less a separate problem, although all are dependent on one another. The light sense is the faculty of perceiving light and recognizing gradations in its intensity. It can also be described as the fundamental response of the retina to changes in its adequate stimulus, i. e., light. The color sense is a modification of the light sense in that one is enabled to discriminate between the different wavelengths of the spectrum. The form sense is the ability to discriminate a contour. It is the faculty by which one perceives the shape of objects, and it depends on the ability of the retina to distinguish between excitation and nonexcitation. It is therefore a higher development of the light sense and necessitates intact pathways from a sensitive retina to the brain.

Under a discussion of the light sense the minimum visible is properly considered. It is the least amount of stimulus which, when admitted to the retina, will send a discharge or burst of impulses up the optic nerve. Influence of aberrations in the refractive system of the eye on the minimum visible is next discussed, and is most important. In physiologic optics one is accustomed to speak of "object points" and of "image points." The image point can never be a true point on the retina, even though monochromatic light is used. Every point image on the retina must be a small diffusion circle (taking the form of the pupillary aperture), and the intensity of light in this circle is not evenly diffused, being maximum at the center and gradually fading off toward the periphery. "In other words, even in the case

of the image of a linear source, a large number of retinal cone elements receive stimulation, and it is not possible to think of any one cone or even any one small group of cones as being alone stimulated." Because of the spread of light owing to the optical imperfections in every eye, the actual area of the retina which is stimulated is larger than that formed by the visual angle of the entering light. How much larger this stimulated area actually is will depend on the threshold of light sense of the underlying cones, i. e., their minimum visible.

The influence of sensory adaptation on the minimum visible depends largely on the fact that every sensory end-organ in the body will discharge an impulse only as long as it is being stimulated, and a stimulus is a change in the environment. In order to have continuous excitation, the environment must be continually changing or fresh end-organs must be constantly affected by the stimulus. If the stimulus remains constant and no fresh end-organs are called into play, the state of excitation soon dies down and no impulse is sent up the nerve. Even the normal minute ocular movements play a part here. A light source so feeble that it just appears at the threshold of perception will soon fall below the minimum visible if it remains fixed on a small group of rods and cones. The eye protects itself against this effect of sensory adaptation by never remaining still. Even during normal fixation of a test object the eye moves so that the image is carried through a rather large number of retinal elements.

Gradations of the light sense with changes in the intensity are also of importance in discussing the physiology of the light sense. Adrian and Mathews showed that there is an increased frequency of the impulses in the optic nerve with increasing intensity of stimulation. This means that each receptor responds to an increase in intensity of light by discharging more impulses. It is yet to be learned within what limits a single receptor can change the number of impulses it discharges and whether these account satisfactorily for the known number of steps in discrimination of intensity. The conception of each receptor modifying the nerve impulse with a change in the intensity of the stimulus seems contrary to the old belief in the "all or none" law as applied to all sensory receptors.

Under Adler's description of the form sense, four fundamentals are considered. They are the minimum separable, the measurement of this, the aliming power of the eye and the differences between the minimum separable and the aliming power of the eye. The first is the discrimination of two points as separate points. It depends on the distribution of the retinal elements as, for instance, in the fovea, where the cones are closely packed together, as compared to the periphery, where the cones are less solidly packed and also where the threshold is limited in part by the aberrations present in the optical media. All refractive errors, by causing larger diffusion circles on the retina, work further toward preventing fine discrimination. In this respect, the form sense differs slightly from the light sense as tested by the minimum visible. The threshold of the light sense is determined by the sensitivity of the rods and cones. The threshold of the form sense, however, is modified by many other factors which play but little part in the determination of the first.

The aliming power of the eye is the essential factor in the discrimination of a contour and is therefore of importance in visual acuity as tested with letter charts. This sense has been described in the literature under many different names, which sometimes creates considerable confusion. Duke-Elder spoke of it as the "minimum distinguishable change of contour." Other writers have called it the "displacement threshold," or the "vernier threshold," and Hering carefully distinguished between this sense and the minimum separable by speaking of the former as the *Raumsinn*, or sense of space, and of the latter as the *Auflösungsvermögen*, or resolving power of the eye.

It is generally agreed that displacements in a line can be detected when the shift in the image on the retina is much smaller than the diameter of a cone, and this has occasioned many theories as to how the retina can have such fine discrimination. In the case of the minimum separable the limits of acuity correspond well with the best measurements of the diameters of the foveal cones, and this agrees with the idea that acuity is determined by the fineness of the grain of the sensory end-organs. But it is evident that this is impossible in the case of the aliming

power of the eye. It depends wholly on differences in the fusion of the image in correspondence to the mosaic of the cones as the two appear in the retina.

Of further importance, as Anderson and Weymouth pointed out, is the fact that the eye is in constant motion, even during most exact fusion, so that the image of any line would be swept back and forth over a large number of cones. A sense of course of a percept depends on the number of cones stimulated. These normal movements of the eye would enable one to obtain an extremely accurate perception of any displacement in any part of the line.

The paper is closed with a satisfactory summary. Several of the paragraphs from this summary are included verbatim here because of their importance.

"The threshold of the light sense is termed the minimum visible. It cannot be measured in terms of a visual angle, but only in units of light energy.

"The minimum separable, i. e., the ability to discriminate two separate points, is similar in all respects to the minimum visible except that its threshold value can be expressed in terms of a visual angle, since an unstimulated cone or group of cones must lie between the ones stimulated. It is possible that the close correspondence between the threshold of the minimum separable and the known size of the foveal cones is merely coincidence, since it is doubtful if the images on the retina can ever be limited in actual extent to the diameter of a cone. It is possible that they may be limited functionally, however, in that the light which is spread over adjoining cones falls below the threshold of stimulation. In any event, the threshold values of the minimum separable have never been found less than the diameter of the foveal cones. Both the minimum visible and the minimum separable depend on a difference in brightness.

"The alining power of the eye is the ability to detect a slight change in a contour, and depends not on perception of brightness alone but on other unknown factors. It is possible that this sense, which is far more acute than the minimum separable, is mediated by an averaging process whereby a large number of retinal elements are stimulated. Further studies should be made to compare the alining power with the minimum separable, especially to note if the type of fixation of the eye is different during the two types of discrimination.

"Visual acuity, as tested with the Snellen charts, is not a test of the various retinal functions alone but involves many other physiologic and psychologic factors. The discrimination of a letter is not a test of the minimum separable alone but involves also the alining power of the eye. It is erroneous, therefore, to regard the 1 minute standard which was set for the size of each part of the letter as having a physiologic basis. The alining power of the eye is far more sensitive than this, and actual practice shows that contours, such as letters, can be discriminated by the normal eye when they subtend a visual angle of much less than 1 minute."

SPAETH, Philadelphia.

THE DENIAL OF THE VAGINA. KAREN HORNEY, Internat. J. Psycho-Analysis **14**:57, 1933.

The fundamental conclusions to which Freud's investigations of the specific character of feminine development have led him are: (1) that in little girls the early development of instinct takes the same course as in boys, both in respect to the erotogenic zones (in the two sexes only one genital organ, the penis, plays a part, the vagina remaining undiscovered) and also in respect to the first choice of a love-object (for both the mother is the first love-object); (2) that the great differences which exist between the two sexes arise from the fact that this similarity of libidinal trend does not go with similar anatomic and biologic foundations. From this premise it follows logically and inevitably that girls feel themselves inadequately equipped for this phallic orientation of their libido and cannot but envy boys their superior endowment in that respect. In addition to the conflicts with the mother which the girl shares with the boy, the girl adds a crucial one of her own; she lays at her mother's door the blame for her lack of a penis. This conflict is crucial because it is this reproach which is essential for her detachment from her mother and her turning to her father.

Hence Freud has chosen an apt phrase to designate the period of blossoming of childish sexuality, the period of infantile genital primacy, in girls as well as in boys, which he calls the "phallic phase."

These statements by Freud lead obviously to certain implications, one of which is that homosexuality is more frequent and common among women than among men. Women fall back more readily than men into a homosexual attitude. The little girl first turns to a man, her father, to bridge a gap of resentment against her mother. Since she cannot have a penis, the child turns to the father in order to receive a child. Hence, of course, the natural desire for motherhood. The author believes that none of these theories can be accepted as true until careful analytic observations are available on the development of normal children. She takes issue with Freud's statements that a clearly defined differentiation between the male and the female characters takes place at puberty. She has been struck by the marked way in which little girls between the second and the fifth year exhibit specifically feminine traits.

Another premise made by Freud is also doubted by the author. Freud assumed that the girl's early genital sensations and activities function in the clitoris. The author believes that vaginal masturbation is just as common as clitoral. This can be proved by frequent observations of signs of vaginal irritation in children, the frequent introduction of foreign bodies into the vagina and the fairly common complaint of mothers that their children put their fingers into the vagina. This is also confirmed by gynecologists, such as Wilhelm Liepmann, who state that in the first years of childhood vaginal masturbation is more common than clitoral. The author finds in her analysis of neurotic women that in the manual genital masturbation the clitoris is more commonly selected than the vagina, but spontaneous genital sensations resulting from general sexual excitations are more frequently located in the vagina. She believes that the child perceives vaginal sensations early in life, as evidenced by fantasies of rape and also by symbolizations in dreams. The reason why the patients deny the existence of vaginal sensations in infancy is because when the patients were children and indulged in masturbation they were led by vaginal sensations to the discovery of the vagina itself, and this resulted in the feeling of anxiety that they made a hole where no hole ought to be. This also accounts for the fact that little girls stop masturbation much sooner than boys. In the discovery of the vagina the little girl conceives that she has done a terrific harm to herself in that region and so she stops masturbating or else restricts this to the clitoris. This anxiety in little girls later results in the denial of the vagina with frigidity. The anxiety associated with the discovery of the vagina proceeds from fantasy of the child about her father's sexual organs, from her observation of menstruation in adult relatives and from the fact that she does not know what harm she has done to herself by masturbation. As she cannot see her own sex organs in the way that a boy can, she fantasies that she might have done herself a great deal more harm than the boy. All these considerations favor the hypothesis that behind the failure to discover the vagina there is a denial of its existence. The denial focuses the attention of the little girl on her clitoris, with many dreams and a strong penis-envy.

The denial of the vagina, of course, is one of the most important factors in frigidity. The woman who denies the vagina recoils from the pleasure associated with coitus.

KASANIN, Howard, R. I.

THALAMENCEPHALOMESENCEPHALIC ORIGIN OF OCULAR SIGNS IN EXOPHTHALMIC GOITER. H. VIALLEFONT and R. LAFON, Ann. d'ocul. **171**:495 (June) 1934.

Viallefont and Lafon limit their paper to a discussion of whether the ocular signs of exophthalmic goiter are not a manifestation of thalamencephalic disturbances. In recalling the following classic ocular signs of exophthalmic goiter, the authors believe that they can be interpreted as neurologic manifestations resulting from a disturbance of the motor tonic or sympathetic nervous centers.

Exophthalmos seems to be dependent on the modification of the tonus of the extrinsic muscles innervated by the sympathetic system. It has been noticed in cases of organic lesion of the central nervous system, particularly in cases of

epidemic encephalitis. Retraction of the upper eyelid is a sign of hypertonia of the elevator muscle; therefore, the retardation of inhibition explains Graefe's sign. Joffroy's sign shows an asynergy between the frontal and the elevator muscles of the eyelid. The tremor of the closed eyelids has all the characteristics of tremor occurring in Parkinson's disease. The infrequency of winking is similar to the facial expression and rigidity present in diseases of the extrapyramidal tract. Möbius' sign or paresis of convergence (paralysis of function) suggests a central lesion. Gifford's sign (difficulty in everting the upper eyelid) points to a disorder of tonus. The lacrimation frequently noted can be compared with the salivation and excessive secretion of saliva observed in encephalitic patients; it has been compared to paroxysmal lacrimation occurring in cases of hysteria and of tabes (Morax). Pigmentation of the eyelids (Jellinek's sign), bleaching of the eyelashes (sometimes noticed) and congestion of the anterior segment (Topolanski's sign) apparently are associated with disorders of the sympathetic nervous system.

The majority of these signs may be interpreted as disturbances of the tonus of the ocular and palpebral muscles comparable to those observed in Parkinson's disease and diseases of the extrapyramidal tracts or of the hypothalamic centers.

The ocular signs of exophthalmic goiter should not be considered as necessarily associated with that disease. Viallefont and Lafon believe it is an expression of a thalamencephalomesencephalic lesion, no matter what the origin. The authors do not know what mechanism in exophthalmic goiter affects the mesencephalothalamencephalon. They do not know whether the hyperthyroidism should be considered as primary or whether the thalamencephalic disturbance is responsible for hyperthyroidism. In certain cases the presence of a true thyrotoxic encephalitis must be considered. It must be admitted that in the case of primary thyrotoxicosis there is an elective action on the thalamencephalomesencephalic regions. The authors recall the studies of Hirsch, who, on examining the content of iodine in the cerebrospinal fluid, found the relative and absolute iodine content increased in cases of exophthalmic goiter. They also direct attention to the research of Schittenhelm and Eisler on the effect of thyroxine on the midbrain; thyroxine appears first in the midbrain and is at once stored in the vegetative centers of that region. Following the administration of thyroxine, these regions are richer in iodine; the other regions of the nervous system are not influenced by the administration or the suppression of thyroxine.

Recently, Israel and Jacob recalled the efficacy of using an extract of the posterior lobe of the hypophysis in certain cases of exophthalmic goiter. Hypophyseal hormones, reaching the third ventricle, may influence, in addition to the adjacent centers regulating sleep and metabolism, the nearest motor centers (e. g., tonus, involuntary motility and voluntary motility), and in consequence may produce tremors or paralyses of the ocular muscles (functional oculomotor paralyses or disturbance in the third nerve).

In conclusion, Viallefont and Lafon stress the fact that the ocular signs of exophthalmic goiter apparently reveal disturbances which may be interpreted as signs of localization in the mesencephalothalamencephalic region.

BERENS, New York.

THE STRUCTURE OF THE CEREBRAL CORTEX: I. AREA ENTORHINALIS. R. LORENTE DE NÓ, J. f. Psychol. u. Neurol. **45**:381, 1933.

During the past ten years Lorente de Nó has been studying the structure of the various regions of the cerebral cortex in different animals. In this paper he describes the structure of the regio entorhinalis. He begins with this region on account of the simplicity of its structure. It was studied in the following animals: the mouse, rat, rabbit, cat and monkey (Nemestrimus and Macacus) and man. Because the same plan of structure has been found in each one of these, only the mouse and monkey are referred to in this paper. The methods employed were those of Nissl, Cajal and Golgi-Cox in the rabbit and monkey and of Golgi in the mouse and cat. As the methods of Golgi and Golgi-Cox do not give constant results, it was necessary to use several hundreds of brains.

The author's conclusions may be summarized as follows: The stratification proposed by Cajal in 1901 has been found to be correct. Every detail of the description by Cajal has been confirmed, and some new facts have been added. Several unknown types of cells have been described, of which the most important are the deep pyramids, the efferent cells of the sixth layer and numerous types of cells with short axis-cylinders. The cortex of the regio entorhinalis receives three kinds of corticopetal fibers running through the white substance and another kind of association fibers arriving through the plexiform layer from the adjacent fields of the allocortex. The cells are arranged in six layers, each of which is characterized by having special cells, a special protoplasmic plexus and a special fibrillar plexus; often the terminal ramifications of the short axons do not extend beyond the layer which is the site of origin of the cell body from which the axon is derived.

The embryologic development of the cortex was investigated and the significance of Brodmann's tectogenetic principle of stratification is discussed. This principle is not an embryologic one but is based on the appearance of the secondary characteristics of the cortex, after each layer and each cell have acquired their fundamental properties. It cannot, therefore, be considered as a sound basis for dividing the cortex in layers, so a revision of the layer division as proposed by the cytoarchitectonic school is absolutely necessary.

The division of the cortex into layers will always be an anatomic problem, because (1) every layer contains, in addition to its own cells, dendrites of the cells from adjacent layers; (2) most of the cells occupy several layers, and (3) the layers cannot be considered physiologic units.

An attempt is made to explain how nerve impulses travel through the cortex; the concept of "closed self-reexciting neuron chains" is developed in order to explain autogenous cortical activity. This mechanism must be the same all through the nervous system, even in the simplest reflexes. The elementary units in the nervous system are not single neurons but consist of chains of neurons linked together in a different fashion for each particular function but always similar to the chains of neurons in the entorhinal cortex.

The entorhinal region represents one of the simplest types of cortex; in the mouse only thirty well defined types of cells can be differentiated in this cortex, whereas in another cortical region (*22* according to Rose's classification), which is that of highest structural complex in this animal, more than sixty cell types were found. At the present time a comparison of the layers in both of these regions is still impossible; as a matter of fact, a comparison of the types of cells is extremely difficult. Several types are common to both regions, but there are types in area *28* which seem to be absent in area *22* and conversely.

KESCHNER, New York.

MUSCULAR DYSTROPHY AND ATROPHY: CLINICAL AND BIOCHEMICAL RESULTS FOLLOWING THE ORAL ADMINISTRATION OF AMINO-ACIDS. CARLO J. TRIPOLI and HOWARD H. BEARD, Arch. Int. Med. **53**:435 (March) 1934.

In treating patients with various forms of muscular atrophy and dystrophy with amino-acids, Tripoli and Beard prefer glutamic acid to glycine because the former constitutes a larger proportion of muscle protein than glycine and because it is cheaper, less toxic and more efficient in forming creatinine. They classify these disorders into the primary muscular myopathies and progressive nuclear muscular atrophy, the latter including progressive spinomuscular atrophy, posterolateral sclerosis and bulbar palsy. Six cases are presented, three in each group. The patients in the second group were classified as follows: (1) a patient with progressive spinomuscular atrophy who showed some improvement in muscular strength and diminution in twitchings following a course of treatment with glycine (10 Gm. daily); (2) a patient with amyotrophic lateral sclerosis who showed slight improvement in muscle tone following oral administration of glutamic acid (10 Gm. daily in milk), and (3) a patient suffering from amyotrophic lateral sclerosis who showed no significant improvement after a prolonged course of glutamic acid therapy. Much better results, however, were obtained in the group with dystrophy.

These patients received glutamic acid daily (10 Gm.) in milk. They are classified as follows: (1) a man who had suffered from pseudohypertrophic muscular dystrophy for twenty-three years, and who after ten weeks of treatment with glutamic acid, glycine and ephedrine began to gain weight, exhibited a more stable gait and experienced better muscular control generally; (2) a woman who had suffered from functional atrophy of the legs subsequent to a protracted period of rest in bed, and who made a substantially complete recovery following a few weeks of glutamic acid therapy, and (3) a man who had suffered for twenty-one years from progressive muscular dystrophy, and showed marked improvement after one month of treatment with glutamic acid; his wobbling gait disappeared, he was able to walk miles without fatigue and he gained markedly in weight.

Reviewing the literature, the authors point out that in patients with muscular dystrophy improvement has generally been reported following therapy with amino-acids. Pseudohypertrophic muscular dystrophy, myasthenia gravis and progressive muscular dystrophy, in particular, are improved by the administration of glycine or glutamic acid. On the other hand, patients with atrophy suffering primarily from lesions of the spinal cord are little affected by treatment with amino-acids. They suggest that such therapy may have some value, however, in the acute and convalescent stages of infantile paralysis, by preserving the tone of the paralyzed muscles until regeneration of the affected nerves occurs. The biochemical explanation for the formation of creatinine from these amino-acids is demonstrated by chemical equations and structural formulas.

DAVIDSON, Newark, N. J.

BODILY DISEASES IN MENTAL DISORDERS. ARTHUR J. HALL, Brit. M. J. **1**:133 (Jan. 27) 1934.

This paper deals with the extent and the modification of the ordinary bodily diseases when they occur in persons suffering from mental disorders. Many of the usual clinical symptoms are absent in patients with mental diseases, and diagnosis is often difficult or even impossible. Of all the usual symptoms of illness, pain is most frequently absent. In cases of intracranial tumor, the absence of indicatory symptoms is noticeable. At postmortem examinations in a general hospital it is unusual to find an intracranial tumor the existence of which has never been suspected during life. In hospitals for mental diseases this is by no means rare. Four cases of undiagnosed tumors in mental patients are cited. The clinical picture of intrathoracic lesions in cases of mental disorder is often different from that in normal persons. This is particularly pronounced in cases of new growths. In cases of lobar pneumonia the signs in the chest, the course of the pyrexia, the pulse-respiration ratio and the occasional herpes febrilis are all there, but pain, cough, general distress and, most of all, restless sleepless nights may be entirely absent in a patient suffering from a mental disease. Of two other common thoracic conditions, tuberculosis and cardiovascular disease, Hall has not as yet collected sufficient information to give details. Considering the large number of necropsies in which gross cardiovascular changes are found, the rarity of anginal pain among patients in hospitals for mental diseases is surprising, and the comparative absence of coughing in wards for tuberculous patients is noticeable. In cases of serious and even fatal organic disease of the stomach and other abdominal organs there may be no discomfort or vomiting, no tenderness on pressure, no local signs and, most surprising of all, no loss of appetite.

The frequent absence in these patients of reflex actions, such as coughing and vomiting, when one would expect them to be present, suggests that they are not such simple actions as they seem, and that when their occurrence might reasonably be attributed solely to a lower reflex mechanism concerned with the particular area affected, centers at a higher physiologic level play a larger part in the act than is usually supposed. The symptom most commonly absent is pain. In some cases it may be that there is an actual deficiency of available receptive material. In others it may be that the receptive material is there but is fully occupied in dealing with other and stronger stimuli. There is also the possibility that a painful

stimulus may be converted into something not painful, as in Pavlov's experimental dog in which a painful electrical stimulus when made part of a conditioned reflex for feeding caused no signs of pain but merely those of anticipatory pleasure.

FERGUSON, Niagara Falls, N. Y.

PARALYSIS OF DIVERGENCE. WILLIAM H. STOKES, Arch. Ophth. **11**:651 (April) 1934.

In the available literature to date there have been fifty recorded cases of paralysis of divergence. It is, however, possible that many are overlooked and pass unrecognized, because Duane himself saw nine of these instances and Alger the same number. Stokes, who reports five cases, observed two in the same family—in sisters, 68 and 71 years of age, respectively. In case 4, the paralysis apparently disappeared two months after its observation, while the paralysis in case 5 was complicated by an excessive convergence. The five cases are reported in detail.

From the standpoint of etiology, the most interesting point relative to paralysis of divergence is the rôle which the etiology plays in regard to the presence of a divergence center. Some observers do not agree that such a cerebral center exists; they think that divergence, as a form of ocular motility, is merely a relaxation of the internal rectus muscles. In cases of paralysis of divergence it seems certain that an organic lesion of the brain is the causative factor. This paralysis has been reported in association with acute poliomyelitis, following diphtheria, following pleurisy on the left side, as a sequel of influenza, in the course of syphilis, in various intoxications of the central nervous system, such as lead poisoning and uremia, following injuries to the brain and trauma causing edema and hemorrhage and in diseases of the blood vessels in the form of hemorrhage, thrombosis or embolism.

In part the conclusions of Stokes are: 1. Paralysis of divergence is perhaps the rarest of all conjugate palsies, but the condition is not so rare as the number of reported cases indicates. 2. It should be looked for in all instances in which there is homonomous diplopia. 3. The diplopia field taken both for distance and for near vision is clearly differentiating. 4. The diplopia may be temporary or permanent. 5. If it is permanent, the diplopia for distance should be corrected with prisms placed base out to produce binocular single vision, provided the amount of diplopia is slight and there is no complicating excess of convergence. Prisms should not be ordered for near vision. 6. If the diplopia is too great for satisfactory prismatic correction, operative measures should be instituted, preferably a resection or advancement of both external rectus muscles. 7. Occlusion of one eye by means of a frosted glass or black disk does not seem to give satisfactory relief from headaches, vertigo, nausea and an apparent movement of objects noticed by the patient, because there may still be an interference with monocular projection.

SPAETH, Philadelphia.

STATUS DYSRAPHICUS. F. CURTIUS and I. LORENZ, Ztschr. f. d. ges. Neurol. u. Psychiat. **149**:1 (Dec.) 1933.

Status dysraphicus is characterized by a disproportion between the trunk and the limbs, bending of the vertebrae, deformities of the fingers, funnel breast, clubfoot, anomalies of the mammary glands, sensory and reflex disturbances of the extremities, acrocyanosis and enuresis. The characteristics of status dysraphicus are referable to a disturbance in the embryonal closing of the medullary tube. For this reason it is valuable in the understanding of nervous diseases, particularly syringomyelia, since newer studies show that this disease is the result of a dysraphic mechanism.

Curtius and Lorenz subjected patients with status dysraphicus in their clinic to study with the following points in mind: (1) whether other characteristics of this disorder were present so that it might be established as an entity; (2) whether there could be established a definite connection between syringomyelia and status dysraphicus, and (3) whether a more general neuropathologic morbidity could be established through status dysraphicus.

The cases of thirty-two patients were investigated. It was established that status dysraphicus is not only an embryologic entity but a clinical one. This was confirmed in thirty of the thirty-two cases. Spina bifida occulta was found in 17.3 per cent of the patients and in bedwetters the incidence rose to 59.5 per cent. Many of the patient presented neurologic symptoms—twenty-one of thirty-two; sixteen showed mental peculiarities. Often there was a neuropathic condition in the family. There was a close relation between status dysraphicus and syringomyelia. In eight of eleven patients with syringomyelia there was spina bifida occulta; in six families with syringomyelia there were dysraphic disturbances, and ten of the seventeen patients with syringomyelia were mentally abnormal.

The origin of status dysraphicus is only partly clear. That it is a relatively sharply defined developmental anomaly is evident. There is a good deal of uncertainty concerning the clinical symptoms and concerning the clinical symptom complex and its relation to other nervous diseases. There is a close connection between status dysraphicus and the heredodegenerations.

ALPERS, Philadelphia.

PRESENT CONCEPTIONS OF THE ORGANIC AND THE FUNCTIONAL IN NEUROPSYCHIATRY. JACQUES VIÉ, Hyg. ment. **29**:45 (March) 1934.

This article gives a comprehensive discussion of the varying concepts centering about the terms "organic" and "functional." During the nineteenth century, the great developments of anatomicoclinical methods resulted in a firm base for the idea of "organicity." Babinski sought diligently for pathognomonic signs of organicity, and for a long time this general point of view prevailed. More and more have recent discussions thrown doubts on these positions. One of the most interesting contributions is that by Claude, Baruk and Nouel, in 1929, who challenged the old idea of organicity as related to noneffect of the will. In cases of catatonia there are certain negativisms and movements which are fairly clearly under the control of the will. Associated with these are vasomotor and secretory disturbances capable of experimental reproduction and not reducible by psychotherapy. Such complex intertwinings are becoming increasingly known, so that no longer must one accept the effect of will or of psychotherapy as a criterion of organicity or nonorganicity. If such differentiations are to be made, they must be on the basis of intensity of sign and symptom rather than on that of their nature. The same is certainly true of epilepsy; no longer can it be regarded as "functional" or as "organic." Rather it is a continuous series from "more organicity" to "less organicity."

In summary, Vie regards the present idea of the organicity of a symptom as best described by the triple criteria of: (1) an anatomophysiologic disturbance in a segment or segments of the neuraxis; (2) the existence of a morbid symptomatology which necessitates explanation on an anatomophysiologic disturbance, and (3) the materiality of the etiologic factor, with confirmation in effects from treatment. As a corollary, he would establish three categories of morbid phenomena: (1) lesions essentially morphologic in character; (2) morbid functional disturbances, at least mainly organic in nature, and (3) reactional modalities, essentially psychologic.

ANDERSON, Los Angeles.

A CONTRIBUTION TO THE GENETIC STUDY OF MENTAL DEFICIENTS. L. S. PENROSE, Brit. M. J. **1**:10 (Jan. 6) 1934.

A family history is described in which mentally normal children are the offspring of an incestuous union between a brother and a sister of low mentality. The brother and sister were the fifth and the eighth born in a family of eight children. One of the mother's sisters was said to have been subject to epilepsy, and a great-great-nephew, who was also epileptic, was certified as feebleminded. A sister of the incestuous couple was regarded as mentally dull. She married a first cousin once removed (on the mother's side) and had eleven children, all of whom were

said to be capable and intelligent. The incestuous couple remained together as man and wife for fifteen years. Three children were born to this union; one died at the age of 2½ years. The brother was in a mental hospital suffering from dementia paralytica, and his general intelligence is reported to have appeared definitely subnormal before the onset of dementia; the sister was certified as mentally defective; the Wassermann reaction was negative; with standardized mental tests, her mental age was about 8 years and her intelligence quotient was between 50 and 60. The oldest child of this union was brought up in an institution from the age of 13; the impression he gave at that time was particularly favorable, and he was considered much above the average of the children then in the home; his school reports were always good; he had earned his own living continuously since leaving school; there were no reports of standardized tests of his intelligence. The younger child was brought up in an institution from the age of 3; he was considered a nice boy, quick in response, amiable and sensible in conversation; standardized tests give him a mental age between 7 and 8 years with a chronologic age at the time of testing of 7 years and 7 months. Blood grouping tests of the parents and of the children indicate that the children are the result of the incestuous union; there has been no evidence to suggest that there might be a father of the children other than the brother of the mother.

FERGUSON, Niagara Falls, N. Y.

BLEPHAROSPASM WITH INCOMPLETE CLOSURE OF THE LIDS AND WITH PSEUDO-PARADOXICAL SYNKINESIS OF THE FRONTAL MUSCLES IN A MAN FOLLOWING ENCEPHALITIS. BEPPINO DISERTORI, Rev. d'oto-neuro-opht. **12**:190 (March) 1934.

A man, aged 22, had suffered for two years with blepharospasm, which followed an attack of epidemic encephalitis ten years previously. During the attacks the lids were not completely closed. Accompanying the spasm there were intense tonicoclonic contractions of the frontal muscles, and the head was bent backward in the attitude of a patient with bilateral ptosis. The patient was able to control the synkinesis of the frontal muscles by an effort of the will, but not that of the orbicularis oculi muscle. The cause of the incomplete closure of the lids was not the frontal synkinesis, because the palpebral slit remained the same even when the spasm of the frontal muscles was inhibited; it must be attributed to a dyskinetic and dystonic disturbance of the orbicularis oculi muscle. The spasm of the frontal muscles was paradoxical only because under normal conditions they never act in synergy with contractions of the orbicularis oculi muscle. In this patient the contraction of the frontalis muscle is an action, useful to the organism, which has become automatized; thus the synkinesis becomes falsely paradoxical. Ordinarily in cases of postencephalitic blepharospasm the lids are firmly closed.

The treatment suggested is the energetic use of intravenous injections of methenamine and sodium salicylate and the bilateral application of roentgen rays to the striomesocephalic region. High voltage roentgen therapy has been found useful in Basta's clinic in ameliorating both the subjective and the objective symptoms in cases of postencephalitic parkinsonism. DENNIS, San Diego, Calif.

FACTORS INVOLVED IN THE PRODUCTION OF SKELETAL MUSCLE PAIN. S. PERLOW, P. MARKLE and L. N. KATZ, Arch. Int. Med. **53**:814 (June) 1934.

To appraise the factors involved in skeletal muscle pain, the authors studied ten young subjects. The arm was exercised by repeated clenchings of one hand, and the leg, by extending a foot against a load. In each case the rate of movement was 60 a minute. Stasis was produced by a sphygmomanometer inflated to the point of diastolic pressure; ischemia, by inflating the cuff to a point well above systolic pressure. Anoxemia (generalized) was produced by requiring the subject to inhale various gas mixtures. Neither complete ischemia nor exercise alone led

to pain, but the combination did. If the ischemia is effected five or ten minutes before the beginning of exercise, pain will occur more promptly than when the two begin simultaneously. If, before pain develops, the exercise stops and the ischemia continues, pain will be experienced. General anoxemia alone did not lead to pain, but when this was associated with circulatory stasis pain became unbearable. It appears that if ischemia is to be an important element in the production of pain in an exercising muscle, the anoxemia must be severe. When both stasis and anoxemia are maintained, pain abates more slowly than when they are relieved.

These studies led the authors to believe that the pain-producing factor is a chemical substance. It appears to have the following properties: It is formed during muscle metabolism, both during exercise and during rest; it is diffusible into the blood stream, by which it can be carried away; in the presence of adequate oxygen, it can be changed into a harmless substance; interference with its removal or with its oxidation will lead to its accumulation in the muscles.

DAVIDSON, Newark, N. J.

THE ANTAGONISTIC EFFECT OF ALCOHOL ON PITUITRIN HYPERGLYCEMIA. M. M. MURRAY, J. Physiol. **77**:247 (Feb. 8) 1933.

In a series of experiments on normal human subjects, Edkins and Murray (1931) showed that the ingestion of alcohol with dextrôse decreased the degree and duration of hyperglycemia. Hunt (1930), in diabetic patients, showed that alcohol definitely decreased hyperglycemia. In the experiment on normal subjects the degree of hyperglycemia, when alcohol and sugar were taken together, seemed to be related to the amount of diuresis. When the hyperglycemia was small, the diuresis was great and vice versa. As a result of this relationship, a suggestion was made that a possible explanation might be that alcohol inhibits the secretion of the posterior lobe of the pituitary gland, or in some way prevents the development in the body of its ordinary action. Injections of a solution of an extract of this lobe are known to produce hyperglycemia and also antidiuresis, or diuresis according to the conditions of the experiment. In a more recent paper, Murray (1932) showed that the ingestion of alcohol antagonized the effect of injection of solution of pituitary on diuresis in normal human subjects, and in anesthetized cats it diminished the diuretic response. The experiments described in the present paper were designed to test the effect of alcohol on the hyperglycemic response to injections of this drug. Murray found that alcohol administered to cats by mouth or intravenously, so that a concentration of over 100 mg. per hundred cubic centimeters of blood is attained, prevents the rise of blood sugar which normally results from the injection of solution of pituitary.

ALPERS, Philadelphia.

PROGNOSIS IN MANIC-DEPRESSIVE PSYCHOSIS. REGINALD R. STEEN, Psychiatric Quart. **7**:419 (July) 1933.

This study deals with 493 patients admitted to a state hospital with a diagnosis of manic-depressive insanity. Only those who were discharged as recovered or who remained in the institution three or more years and were there at the time of study are included in the report. The former are designated the recovered group, and the latter, the chronic group, presumably permanently psychotic for prognostic and practical purposes. Eighty-one per cent of the 493 patients were in the recovered group, and 19 per cent in the chronic group. No significant correlation of body type, frequency of previous attacks, duration of psychosis before admission or family history was found between the two groups. The age at which the first attack occurred varied in the two groups; in the recovered group, 50 per cent of the patients had their first attack before the age of 30, while in only 38 per cent of the chronic group did the onset fall within this age period. More than 53 per cent of the recovered group were free from delusions or hallucinations, whereas only 34 per cent of the chronic group were of this "typical manic-depressive" pattern.

All of the patients who showed stuporous reactions recovered. A study of the personality types, by Hoch's technic, showed a surprising result. The "open" type of personality was more frequent in the chronic group (35 per cent) than in the recovered group (21 per cent). The shut-in type was distributed equally (33 per cent in each) in each group. However, 40 per cent of the recovered group and only 30 per cent of the chronic group have a "normal" (Hoch) personality.

DAVIDSON, Newark, N. J.

PAINFUL PAROXYSMAL HEREDITARY AKINESIA. A. E. KOULKOV, Encéphale **29**:100 (Feb.) 1934.

A clinical entity is described under the name "painful paroxysmal hereditary akinesia." It is regarded as a distinct syndrome not previously described. The essential elements characterizing the condition follow: 1. There are attacks of pain and of weakness in the extremities and in the body, resulting in a total immobilization, associated with light paresis, pain on pressure along the nerve trunks and on the muscles and objective sensory disturbances. 2. The attacks seem to be induced by the absence of food for a period of from five to seven hours, and the gravity of the attacks is in direct relation to the duration of the fast. 3. Localized or generalized fatigue reenforces the attack. 4. No other cause seems to be responsible; there does not appear to be any spontaneous or time-controlled periodicity. 5. The pain ordinarily commences in the roots of the extremities, proceeding to a more diffuse character, and the mental state remains clear, though after the attack there is often an apathetic phase. 6. The duration depends on food; with this comes gradual lessening of pain to complete disappearance in one or two days. 7. In the intervals between attacks the patients appear well.

The disease is hereditary and familial, having been observed in two generations (six cases). The episodes are stereotyped; they seem analogous to, but clinically sharply to be differentiated from, "periodic paralysis" and "migraine." The localization of the pathologic process is an open question, but is linked up with the neurovegetative apparatus. The prognosis is good for life but unfavorable for appreciable amelioration.

ANDERSON, Los Angeles.

A NOTE ON ADMISSIONS TO STATE INSTITUTIONS. HERMAN ADLER, Am. J. Psychiat. **12**:1339 (May) 1933.

Estimates of the incidence of psychoses in a community are usually based on admission rates of hospitals. Adler points out that this is not indicative of the true state of affairs, however, since to some extent admission rates depend on the bed capacities of the state hospitals. When new hospitals for mental diseases are constructed or old ones enlarged, the number and rate of admissions tend to increase until the institutions are overcrowded; at this point a relative stagnation occurs.

Adler also calculates the average age on admission to state institutions of four groups of maladjusted persons. The figures for California parallel closely those for the United States as a whole. The average ages for the entire country are: (1) feebleminded group, 14½ years; (2) delinquent group, 16 years; (3) criminal group, 32¾ years, and (4) psychotic group, 40½ years. Knowledge of the actual age distribution in the feebleminded group shows that this deficiency is detected at an age much lower than the admission age of 14½. What determines commitment is not the existence of feeblemindedness but the inability of the adolescent boy or girl who is defective to adjust in the community as well as does the younger defective child. Adler suggests that a similar factor may operate in the other categories, and that the average age on admission reflects the period at which the subjects become so badly maladjusted as to require institutional care rather than the actual age at the appearance or diagnosis of the problem.

DAVIDSON, Newark, N. J.

HEMATOLOGIC STUDIES IN SCHIZOPHRENIA. PAOLO JEDLOWSKI, Arch. gen. di neurol., psichiat. e psicoanal. **15**:20, 1934.

A study of the blood was made in 171 cases of schizophrenia of various types. In a large majority of cases the blood picture was characterized by considerable lymphocytosis and monocytosis with a more or less pronounced neutropenia. The number of eosinophils, normal in the majority of cases, was increased in about one fourth and diminished in about one fifth of the subjects. The number of basophils was normal in the majority of cases. It was rarely increased and was diminished in 36 per cent of the cases. Myelocytes were fairly rare, being encountered in not quite 17 per cent of the cases. Arneth's index was normal in only 30 of the 171 cases; it was rarely shifted to the right (in 20 cases), while in the majority of cases (71 per cent) it was shifted to the left. The deportment of Schilling's hemogram was nearly identical to that of Arneth's index. Velez' sign of nuclear inversion was positive in 63 per cent of the cases. Numerous tables accompanying the text of this study show that according to the type of dementia praecox the hematologic abnormalities were more prominent in the catatonic group than in the hebephrenic and the paranoid group. Moreover, the changes in the blood were most prominent during the active period of the disease and gradually became less prominent as the disease followed the evolution into the chronic stage. This was especially true in the paranoid group of schizophrenic patients.

YAKOVLEV, Palmer, Mass.

THE SUCCESS AND FAILURE OF SUBNORMAL PROBLEM CHILDREN IN THE COMMUNITY. MYRA E. SHIMBERG and WALLY REICHENBERG, Ment. Hyg. **17**:451 (July) 1933.

In a follow-up study for a five year period of 189 feebleminded adolescents, Shimberg and Reichenberg found that 53 per cent had been definitely successful (working regularly and causing no trouble to the community). Sixty-eight per cent were self-supporting, although the average income was low, $12 a week. The group of persons for whom social-psychiatric recommendations had been carried out showed a 77 per cent rate of success, whereas only 7 per cent of those for whom these recommendations had been ignored made a good social adjustment. Heredity, home conditions, physical make-up, race and the size of the family bore little relationship to the ultimate social outcome. Of those in homes of good economic status 67 per cent succeeded, whereas only 46 per cent coming from poor homes made social adjustments. Those with good personalities and desirable personality traits were more successful than those with personality handicaps. (Of the former group, only 66 per cent succeeded, and of the latter group, 38 per cent.) The factor of supervision is apparently important, since 66 per cent of the adolescents under good supervision made a success, while only 38 per cent of those devoid of any regular supervision succeeded. From this study, it appears that the mentally defective person can be treated so as to become an asset to the community.

DAVIDSON, Newark, N. J.

SUICIDE AND HOMICIDE AMONG THE INSANE COMMITTED TO THE HOSPITALS FOR MENTAL DISEASES. LEVI-BIANCHINI, Arch. gen. di neurol., psichiat. e psicoanal. **14**:205, 1933.

This monographic and abundantly documented study is based on data from Italian hospitals. The average incidence of violent death among patients for a period of thirty years (1901-1032) was 10 per year. Nine per cent of the deaths were due to suicides and 1 per cent to homicide. This is a low figure when one considers that the total population of the hospitals for mental diseases for the first half of 1933 was 77,500. The greatest number of suicides (64.25 per cent) occurred among persons with the delirious forms of psychoses and with schizophrenia. The highest incidence of suicides (73 per cent) occurred during the first year of commitment. Almost all suicides (94.4 per cent) occurred in the first five years of commitment. The absolute maximal incidence of suicide among insane

persons committed to hospitals occurred in the first month. The suicides were slightly more frequent during the cold season (60 per cent) than during the warm season (40 per cent). They were more frequent during the daytime (60 per cent) than during the night (40 per cent). This relation of suicides to the season and the time of the day was the same for those patients who were under constant supervision (50 per cent) and those who were under ordinary supervision (50 per cent). Suicide was twice more frequent among male than among female patients.

YAKOVLEV, Palmer, Mass.

SINGLE-SHOCK EXCITATION AND INHIBITION OF CONTRALATERAL EXTENSION IN THE SPINAL CAT. K. MATTHES and T. C. RUCH, J. Physiol. **77**:258 (Feb. 8) 1933.

Matthes and Ruch found that single afferent volleys are effective stimuli to contralateral extension in the chronic spinal cat, despite the "inertia" of conduction across the spinal cord and the depression of extensor reflexes in the spinal condition. Single-shocked crossed extensor reflexes are typically of short latency. One variety is of small tension, of brief duration and of myographic form not greatly different from the motor twitch and is probably a single asynchronous efferent-volley reflex. In a second variety, a repetitive central discharge is shown by a jerky prolonged mechanical and electrical response and more rarely by excess of reflex over maximal motor twitch tension. The degree of inhibition of the reflex by an ipsilateral single shock depends on the intervals separating the two stimuli. The level of inhibition increases rapidly as an ipsilateral stimulus is approached in time to a preceding contralateral shock, until an optimal interval is reached. Despite its ipsilateral path, inhibition wanes slowly when sampled at intervals by a following excitatory stimulus. Inhibition can be used analytically to distinguish between reflexes of single asynchronous and repetitive central discharge.

ALPERS, Philadelphia.

THE SYNDROME OF THE PREMOTOR CORTEX IN MAN: IMPAIRMENT OF SKILLED MOVEMENTS, FORCED GRASPING, SPASTICITY, AND VASOMOTOR DISTURBANCE. MARGARET A. KENNARD, H. R. VIETS and J. F. FULTON, Brain **57**:69 (March) 1934.

Building on the experimental results of Fulton and his associates, the authors report a clinical case which seems to corroborate the previous observations in animals. Experiments have indicated that reflex grasping may be caused in monkeys by a cortical lesion restricted to the premotor area. The case reported is that of a man, aged 34, who for four years had had focal seizures affecting the left side of the body, increasing rigidity and awkwardness of the left arm with forced grasping, increased reflexes and vasomotor disturbance; a cystic glioma restricted to the right premotor area was removed surgically; recovery took place with persistence of slight spasticity and grasping and marked awkwardness.

The difference in the chronology of symptoms from lesions of the premotor and motor areas is discussed. In view of the fact that the forced grasping of the patient showed consistent variations with changes of position of the body in space, the phenomenon is considered to be among the righting reflexes. The vasomotor disturbances present on the side opposite the lesion speak for representation of the autonomic nervous system in the cortex.

MICHAELS, Boston.

SYNDROME OF PARALYSIS OF THE TRIGEMINAL AND OCULAR SYMPATHETIC NERVES. HENRI ROGER and YVES POURSINES, Encéphale **29**:167 (March) 1934.

The syndrome of paralysis of the trigeminal and ocular sympathetic nerves was described by J. J. Raeder in 1918 as "a syndrome consisting of the Claude Bernard-Horner syndrome associated with neuralgia of the ophthalmic branch of the trigeminal nerve (and eventually of paralysis of neighboring nerves)." The original condition, which involved lesions of the second, fourth and sixth cranial nerves,

was shown at autopsy to be due to a tumor of the middle cranial fossa, involving laterally the gasserian ganglion and the sympathetic fibers uniting the carotid plexus to the trigeminal and the injured cranial nerves. In 1924, Raeder reported four new observations, without verification at autopsy, in which the sympathetic elements were attacked after separation of the various branches. To these observations are to be added cases described by Klauber in 1917, Cord in 1928 and Van Bogaert and Helsmoortel in 1927. Roger and Poursines report six cases, characterized by paralysis of the trigeminal nerve, pain, hypesthesia and the more or less complete syndrome of Claude Bernard and Horner. The etiologic factors may be: cerebral tumors of the middle fossa, developing in or dependent on the meninges; (2) trauma of the cranium, and (3) certain infections, e. g., syphilis, deep osteitis and herpes.

ANDERSON, Los Angeles.

PLASMOCHIN, PLASMOCHIN WITH QUININE SALTS AND ATABRINE IN MALARIA THERAPY. PAUL F. RUSSELL, Arch. Int. Med. **53**:309 (Feb.) 1934.

Because of its expense, slowness of action and unpleasantness and the frequency of idiosyncrasy, quinine is not an ideal drug. Among the antimalarial substitutes proposed is plasmochin, which is a derivative of aminoquinoline. It is marketed in tablets of the hydrochloride salt and is also sold in combination with quinine. In a series of experiments on canaries with malaria, Russell found the combination of quinine and plasmochin more effective than either preparation alone. He found it possible to sterilize the blood of infected birds with seven daily injections of the compound when corresponding doses of each separately proved ineffective. The plasmochin appeared to destroy the plasmodia in the blood, but residual, transmissible infection was invariably present when quinine was not used.

Plasmochin may be used when quinine is contraindicated, as in certain cases of blackwater fever, during pregnancy or in the presence of idiosyncrasy. For adults, the dose is three tablets a day after meals, three successive days each week, until the parasites and symptoms have disappeared. Essentially, however, plasmochin is to be considered an adjuvant to rather than a substitute for quinine.

DAVIDSON, Newark, N. J.

HAEMANGIOMA OF THE SPINE. F. STRONG HEANEY and P. H. WHITAKER, Brit. M. J. **2**:775 (Oct. 28) 1933.

It has been stated that hemangioma of the vertebrae is rare, but Heaney and Whitaker assert that this is true of their clinical recognition but not of their actual occurrence. They are most common in the middorsal region. The case reported is the only one of hemangioma occurring in the cervical region. It came under observation following an accident which led to the serious condition of subluxation at the atlanto-axial joint. Roentgenographic examination revealed that the atlas was subluxated forward on the axis, the odontoid process being bent forward. The normal bone density was not present, and the whole body appeared to be riddled with small spaces, while the remaining bone trabeculation around the spaces was thickened. The condition was localized to the body, odontoid process and laminae of the axis. The diagnosis was a single isolated hemangioma. Roentgen treatment was undertaken, and the symptoms of pain and limited movements were relieved. The bone showed no increased consolidation even after twelve months. As regards prognosis, there seems little hope of being able to dispense with an immobilizing apparatus which prevents the subluxation from becoming a complete dislocation.

FERGUSON, Niagara Falls, N. Y.

THE VALUE OF A NEGATIVE HINTON TEST IN THE EXCLUSION OF NEUROSYPHILIS. ARTHUR BERK and WILLIAM HINTON, Am. J. Syph. & Neurol. **18**:92 (Jan.) 1934.

Seven hundred and eighty-seven patients suffering from syphilis were studied by the Hinton test (of the blood) and by conventional examination of the spinal

fluid. The Hinton test of the blood was never negative in any case of definite neurosyphilis in which the reaction of the spinal fluid was positive; there were 108 such cases. There were 13 cases clinically diagnosed as instances of cerebrospinal syphilis in which the Hinton test of the blood was negative, but in each the spinal fluid also gave a negative reaction. The correlations between positive Hinton tests and cases of cerebrospinal syphilis, however, was not so reliable. It appears, therefore, that a negative Hinton test of the blood, corroborated by repetition, practically excludes the likelihood of any positive evidence in the spinal fluid of syphilis of the central nervous system.

DAVIDSON, Newark, N. J.

CEREBRAL (VENTRICULAR) HYDRODYNAMIC TEST FOR THROMBOSIS OF THE LATERAL SINUS. WALTER E. DANDY, Arch. Otolaryng. **19**:297 (March) 1934.

This article gives a résumé of the information to be gained by the Queckenstedt test as modified by Tobey and Ayer to determine whether lateral thrombosis is present. The danger of lumbar puncture in certain cases of occlusion is well recognized, and Dandy has devised a test in which the puncture is made into the ventricle of the brain, and after jugular compression the condition of the lateral sinus is determined. This, of course, would be applied only in cases in which the ventricular puncture was planned on account of thrombus or abscess of the brain and in which this additional test could be carried out at the same time without the necessity of spinal puncture.

HUNTER, Philadelphia.

STIMULATION OF THE CAROTID SINUS BY PHYSIOLOGIC AND PHARMACOLOGIC STIMULI. K. GOLLWITZER-MEIER, Arch. f. d. ges. Physiol. **234**:342, 1934.

Contrary to the experiments of former investigators, physiologic blood stimuli (change of oxygen, carbon dioxide and hydrogen ion concentration) failed to elicit respiratory reflexes by stimulation of the carotid sinus. Bilateral denervation of the carotid sinus had little influence on the dyspnea in oxygen deficiency. Lobeline acts on the respiration reflexly from the carotid sinus as well as by central stimulation. The receptors for different stimuli have a different location in the area of the carotid sinus; the receptive field for physical stimuli lies in the carotid sinus and the field for chemical stimulation in the beginning of the occipital artery.

SPIEGEL, Philadelphia.

CHIASMIC SYNDROME OF AN ANEURYSM OF THE INTERNAL CAROTID. F. CARAMAZZA, Ann. d'ocul. **170**:696 (Aug.) 1933.

Caramazza observed a patient who presented binasal hemianopia on ocular examination, and postpapillary atrophy in one eye and papillary stasis with hemorrhage in the other eye on ophthalmoscopic examination. Roentgenographic examination showed opacities corresponding exactly to the internal carotid arteries in the region where they course medially to the anterior clinoid processes and laterally to the optic nerves. The case is important, not only because cases are rarely observed in which a diagnosis is made clinically, but also because it was possible to follow the evolution of the campimetric changes from the beginning to the final appearance of a definite binasal hemianopia.

RETINAL HYPOTENSION. BAILLIART and TILLÉ, Ann. d'ocul. **170**:882 (Oct.) 1933.

Bailliart and Tillé studied the pathologic conditions in which they were able to determine retinal hypotension: vascular accidents with retinal lesions, characterized by small white spots (circinate or senile retinitis), optic atrophy with excavation without ocular hypertension and vascular spasms on the disk (epilepsy). They observed several patients with Bravais-Jacksonian epilepsy associated with retinal hypotension on the side of the epilepsy. In retrobulbar neuritis the prog-

nosis is more severe when there is hypotension. Dubar has studied the retinal arterial tension in many epileptic patients and has seen variable tension, often with remarkable instability.

OCULOCEPHALIC DEVIATION PRODUCED BY LESION OF A CEREBRAL HEMISPHERE. G. RAVÀ, Ann. d'ocul. **170**:702 (Aug.) 1933.

Ravà observed that the oculocephalic deviation caused by a lesion of a cerebral hemisphere can be produced by different mechanisms; he maintains, however, that in many cases when the eyes are turned toward the lesion the deviation is produced by the visual sensorial reflex on the normal side, which is no longer counterbalanced by the diseased side, affected with lateral homonymous hemianopia. Oculocephalic deviation caused by hemianopia, according to Ravà, may have certain characteristics which lead one to suspect the presence of the lesion and perhaps to make a diagnosis.

A CASE OF VAN DER HOEVE'S DISEASE. MASPÉTIOL, Ann. d'ocul. **170**:884 (Oct.) 1933.

Maspétiol presents a case of van der Hoeve's syndrome, with a complete symptomatic triad: fragility of the bones, which appeared at puberty, thirteen fractures occurring; bilateral deafness of mixed type with hypo-excitability of the semicircular canals, and marked blueness of the sclera. Opacities of the lens were noted in the anterior cortex. General examination demonstrated hypothyroidism, which indicates the importance of glands of internal secretion in the etiology of this syndrome. Bailliart has stressed the fact that blue scleras are not always associated with the syndrome of van der Hoeve.

PULSATING EXOPHTHALMOS TREATED AND CURED BY LIGATURE OF THE ORBITAL VEINS AT THE ENTRANCE OF THE ORBIT. VALIÈRE-VIALEIX, Ann. d'ocul. **170**:533 (June) 1933.

After unsuccessful treatment by injections of gelatinized serum, Valière-Vialeix performed orbitotomy, with incision in the eyebrow and ligature and excision of the veins. The result was satisfactory. The loss of vision was a result of the orbital fracture which had injured the optic nerve, but the exophthalmos and pain disappeared. Morax said that he had observed a similar case in which the results of the operation were identical. Rochon-Duvigneaud observed the same excellent results in a patient operated on by Cauchois.

DIAGNOSTIC VALUE OF THE IMAGE OF THE SELLA TURCICA, BASED ON SOME INTERESTING CASES. F. MASCHERPA, Ann. d'ocul. **170**:695 (Aug.) 1933.

The technic of examination of the sella turcica has become so accurate that the smallest lesions can be found if the roentgenogram is taken correctly. On the other hand, Mascherpa believes that in certain serious cases of long duration a negative roentgenogram may be obtained, and he has reported some particularly instructive cases. He believes that it is unwise to form conclusions from the examination of the image of the sella turcica unless the findings are in perfect accord with those of the clinical examination.

PUPILLARY REFLEXOMETRY. BUJADOUX and KOFMAN, Ann. d'ocul. **170**:895 (Oct.) 1933.

Bujadoux and Kofman present a new apparatus which registers the reactions of the pupil to light. A series of light stimuli of known progressive intensity are flashed on the iris, and the diameter of the pupil is measured. The findings are plotted. The authors describe a special graph (*graphique en plateau*) noted in the early stages of the contraction of the pupil in association with cytologic changes of cerebrospinal syphilis; this reaction appears to be a phase of pre-Argyll Robertson pupil.

GRAEFE'S PSEUDOSIGN (SIGN OF FUCHS). H. COPPEZ, Ann. d'ocul. **170**:170 (Feb.) 1933.

In the case reported by Coppez, elevation and retraction of the upper eyelid were noted as the eye was rotated downward. This symptom may be partially explained by the fact that part of the nerve fibers in the course of development may not join the muscular groups for which they were originally destined but may supply other muscles. Certain filaments of the third nerve originally destined to supply the right medial and right inferior rectus muscles follow an aberrant course and enter the nerve branches which innervate the levator of the upper eyelid.

THE SYNDROME OF THE BLUE SCLERA: RELATION TO PARATHYROID OSTEOSIS. H. VIALLEFONT, Ann. d'ocul. **170**:289 (April) 1933.

Viallefont concludes that the most evident symptom in this syndrome is the blue color of the sclera. He suggests the importance of parathyroid dysfunction and, in certain cases, the surgical exploration of the parathyroid glands. He is of the opinion that treatment of the parathyroid glands by irradiation does not produce a complete cure, but that it improves the condition of the bones and prevents new fractures.

FINAL RESULTS OF MALARIA THERAPY IN TABETIC OPTIC ATROPHY. D. SABBADINI, Ann. d'ocul. **170**:701 (Aug.) 1933.

Sabbadini reports the results obtained in three cases of tabetic optic atrophy in which the patients received malaria therapy in 1926. In the first case there was a complete cure; in the second case the condition remained stationary; in the third case the condition was slightly worse. Sabbadini asserts that malaria therapy in tabetic atrophy of the optic nerve is efficacious and that mercury, which decreases the beneficial effect of fever therapy, is injurious.

DURATION OF ANGIOSPASM OF THE CENTRAL ARTERY OF THE RETINA: REPORT ON CASES OF RETROBULBAR NEURITIS OF PARANASAL SINUS ORIGIN. E. MORELLI, Ann. d'ocul. **170**:697 (Aug.) 1933.

Morelli followed the different phases of the angiospastic crisis affecting the central artery of the retina in three cases. He maintains that angiospasm cannot last longer than fifteen minutes without causing serious sequelae.

INTERVENTION ON THE HYPOPHYSIS: TECHNIC AND RESULTS. P. CALICETI, Ann. d'ocul. **170**:693 (Aug.) 1933.

Caliceti reports the cases of three adults in whom the pituitary body was removed by the Hirsch-Segura method. Both the immediate and the late results were good. There was marked improvement in the visual acuity and in the general disturbances. BERENS, New York.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Oct. 9, 1934

C. BURNS CRAIG, M.D., *Chairman, Presiding*

THE PORTAL OF ENTRY OF THE VIRUS OF ACUTE ANTERIOR POLIOMYELITIS AND THE PATHOGENESIS OF THIS CONDITION. DR. MAURICE BRODIE, New York (by invitation), and DR. ARTHUR R. ELVIDGE, Montreal, Canada (by invitation).

A study was carried out on the monkey to determine the portal of entry and the subsequent course of the virus of poliomyelitis through the body to its final localization in the nerve cells. At the same time, the disease was studied in human beings, and the two types were correlated.

There is considerable evidence that the virus enters the nasopharynx rather than the gastro-intestinal tract, for it can be found there both in human beings and in experimental animals with the disease and also in carriers, while there is but a single unconfirmed report of its isolation from the feces. Likewise the monkey can be infected easily by the nasal route in contradistinction to the oral route. (In order to determine this point, bilateral section and partial removal of the bulb and tract of the olfactory nerves were carried out in a series of Macacus rhesus monkeys. It was found that although the controls acquired the disease after a single instillation of the virus, the experimental animals resisted multiple inoculations.)

The nasal mucosa is innervated not only by the olfactory nerve but by branches of the fifth and seventh cranial nerves. In addition, the virus can percolate from the nasopharynx to the tonsils with its intact nerve supply. Yet, when the olfactory nerve was cut no infection occurred, which indicates clearly that the first cranial nerve is the only one of the nasopharynx that can transmit the virus of poliomyelitis to the central nervous system. Over a period of from three to four weeks animals received from twelve to fifteen intranasal inoculations, and a considerable portion of the material introduced dribbled to the gastro-intestinal tract. Therefore, since only the olfactory nerves of the nasal cavity can carry the virus and since no infection was obtained when large amounts of virus reached the gastro-intestinal tract, the portal of entry must be the nasal cavities.

When the perineural sheath of the olfactory tract and bulb was blocked with iodine, infection was obtained by the nasal route, suggesting that the virus travels along the nerve fibers to the central nervous system rather than along its sheath.

The fact that the virus travels along the olfactory nerve fibers to reach the central nervous system suggests a direct extension along the nerve tracts to the rhinencephalon rather than a primary general spread. However, the idea of a general dissemination of the virus, either hematogenous or lymphogenous, has received almost general recognition by clinicians.

Therefore, the blood of each of 4 animals which had been infected by the intranasal route was tested for the presence of virus during the incubation, preparalytic and early and late paralytic stages of the disease, but in no instance was the presence of virus demonstrated. The filtrates made from suspensions of tissue from almost all of the organs, including the salivary glands, liver, spleen, mesenteric lymph nodes, kidneys and muscles, removed in the early preparalytic stage, failed to show the presence of virus. Likewise, except for the tonsils, we were unable to demonstrate the presence of virus outside the central nervous system in 2 cases in human beings; this exception we believe to be due to the survival of some virus that had entered the nasopharynx. Moreover, histopathologic study of tissue from

the organs of more than 50 monkeys and 7 human beings in the acute stage of the disease failed to reveal the presence of any specific lesions outside the central nervous system. Slight changes were present in the lymphoid tissue. The mesenteric lymph nodes, Peyer's patches and the tonsils showed slight catarrhal inflammation with swelling of the germinal centers, some necrosis of the reticular cells, disintegration of the lymphoid elements and slight infiltration with large mononuclear plasma cells and polymorphonuclear leukocytes. The spleen showed some swelling and disintegration of the reticular cells, while the thymus showed thickening and degenerative necrosis of Hassall's corpuscles, especially in the center, and infiltration with polylobed nucleated cells. These changes are certainly not significant in cases of poliomyelitis, for they may be present in any acute febrile condition. In keeping with the absence of virus in these organs is the fact that the changes were not present in all the cases in which examination was made. Therefore, there seems to be no evidence that the virus of poliomyelitis produces a generalized infection, and so it must travel from the nasopharynx directly to the cerebrospinal axis.

In order to determine whether it traveled by the nerve tracts or by the spinal fluid, the spinal cord of monkeys was severed in the dorsal region and the virus implanted into the upper or the lower segment. It failed to pass the gap to reach the uninoculated segment. Likewise the virus failed to travel along the sciatic nerve when the fibers were cut and the perineural sheath sutured. Thus it appears that the virus travels by the nerve tracts rather than by the spinal fluid. This was further confirmed by the fact that virus was not found in the spinal fluid at the incubation period or at any stage of the disease in monkeys or in the preparalytic stages of the disease in human beings.

Transmission of the disease by the nerve tract was not due to any neurotropic qualities that the fixed virus had gained through serial transmission in monkeys, for a recently isolated virus gave similar results. Transmission along the nerve fibers presupposes that the virus was carried directly to the neurons, where it would cause damage to the nerve cells, and so the infiltration would be secondary. Several experimental studies confirmed this.

On investigating the reason for the predisposition of the virus for the spinal cord we found that the brain had an antiviral action not possessed by the cord. In fact, it seemed that the cord actually absorbed the virus.

Although this work, along with that of others, indicates clearly that experimental poliomyelitis is entirely a disease of the central nervous system and the virus travels along the nerve tracts and that the disease probably propagates in the same manner in human beings, the preparalytic stage and the diphasic type of the clinical disease must still be explained. However, as the experimental disease, which is unquestionably neurotropic, has a similar preparalytic period with fever, which usually precedes either involvement of the central nervous system or pleocytosis of the cerebrospinal fluid, and also shows diphasic types, it is also possible to explain the phenomena in human beings on the basis of early involvement of the central nervous system, perhaps of the midbrain, the hypothalamus or even of the brain stem, as Faber has suggested, rather than on the basis of systemic invasion by the virus. In the diphasic types the quiescent period may be due to a halt of the virus in the central nervous system or to slow progress down the spinal tract until it reaches the anterior horn cells, thus giving rise to the second attack.

So far we have dealt only with cases in which there was definite involvement of the central nervous system; there still remains that group known as abortive cases, which are numerous in epidemics and in which the disease is manifested only by involvement of the gastro-intestinal tract or of the upper part of the respiratory tract, there being no evidence of involvement of the central nervous system. In the experimental animals there occurred light infections of the abortive type, and as in the experimental paralytic form the pleocytosis of the spinal fluid is not the first manifestation of the disease or may occur late in the disease or not at all, absence of pleocytosis does not rule out involvement of the central nervous system. Therefore, we believe that in the abortive cases the virus spreads through

the cerebrospinal axis but produces so little damage that the amount of cellular exudate is insufficient to produce pleocytosis of the cerebrospinal fluid.

These studies explain why treatment with serum is of no value. Since the virus of poliomyelitis is present only in the cerebrospinal axis, which is well insulated from the hematogenous system by the Virchow-Robin spaces, serum would have great difficulty in reaching the virus. If the serum did reach the central nervous system it could not dislodge the virus, which appears to be fixed to the nerve cells, nor could it prevent further propagation of the virus, for viruses grow in tissue culture in the presence of their own antibody. In a certain instance we found that the virus of poliomyelitis spread through the central nervous system in the presence of demonstrable antibody. The serum could not be given before the virus reached the central nervous system because it has been shown by others that in experimental poliomyelitis the nerve cells are damaged before symptoms set in.

ACTIVE IMMUNIZATION TO ACUTE ANTERIOR POLIOMYELITIS. DR. WILLIAM H. PARK, New York.

Since the virus of poliomyelitis was discovered, attempts have been made to produce active immunization. The first investigation concerned the merits of a mixture of vaccine and antiserum. A number of fairly successful attempts have been made since the first results were published in 1910 by Roemer and Joseph. Lately, Rhoads, Goldbloom, Brodie, Kramer and others have been successful in producing immunity in monkeys by the injection of antiserum and vaccine either together or separately.

Vaccination with Doses of Vaccine, the First of Which was Heated to 55 C. and the Last to Blood Heat Only.—The most successful early results were obtained by Abramson and Gerber in 1917 and 1918 in the research laboratories of the department of health of New York. They obtained considerable success in the following way: The emulsion of the spinal cord was heated at 55 C. for thirty minutes on the first two days and then at 45 and 37 C. on the third and fourth days and was injected without preliminary heating on the fifth day. All the animals remained well. Five of the 8 monkeys resisted the injection of a multiple fatal dose.

A large series of similar tests were carried out by Shaughnessy, Harmon and Gordon in 1930.

Attenuation by Chemicals.—Kraus, in 1910 and 1911, reported the results of treating the virus with phenol in a concentration of from 1 to 1.5 per cent. He found that this vaccine gave protection to animals, but others were unable to verify his results. However, in 1930 Kraus confirmed his earlier work.

Sodium ricinoleate was used by McKinley and Larsen in 1926. The results were fairly satisfactory, but the authors considered they had used too few animals to justify the use of the drug as a vaccine for human beings.

Formaldehyde.—Early attempts were made with formaldehyde-treated virus by Römer, by Abramson and Gerber and by Jungeblut. In 1932 Brodie began to make a more thorough study of the value as a vaccine of the virus killed by formaldehyde. In 1933 he continued his experiments in New York, and the results here reported are of his work and that of his assistants. It is believed that a practical and safe vaccine has been developed. In his work at Montreal Brodie found that the injection of a suspension of infective cord inactivated with a 0.3 per cent solution of formaldehyde would immunize monkeys against the virus of poliomyelitis. However, owing to this concentration of formaldehyde the animals had considerable irritation and necrosis of the skin.

Tests were then carried out with virus suspensions inactivated with lower concentrations of formaldehyde, and inactivation was carried out at incubator rather than at icebox temperature. It was found that 0.2 per cent formaldehyde inactivated the virus within six hours and 0.1 per cent, within twelve hours, and that virus suspensions treated in either way were antigenic, for the majority of the animals acquired both tissue and humoral immunity. The antigen prepared with 0.1 per cent formaldehyde gave practically no cutaneous irritation.

It was found that virus inactivated at icebox temperature was no less antigenic when contact between the virus and the germicide was maintained for a week longer than necessary for inactivation at 37.5 C. On the other hand, when inactivation was carried out at incubator temperature for a longer time than necessary the antigenicity of the preparation was reduced.

It was now decided to test the applicability of this vaccine for the protection of human beings. However, before it was given to children it was decided to test it on some of the staff of the research laboratories so as to determine whether or not it gave any unpleasant local or general reactions and also to test its ability to produce antiviral substances. Accordingly, 6 volunteers from the bureau of laboratories of the New York department of health were given the vaccine.

As this trial and the numerous animal experiments showed that the vaccine gave no harmful results, it was decided to apply it to 12 children. Five children received a single dose of vaccine, and 7 were given two doses, spaced thirteen days apart. Each dose consisted of 5 cc. of a 10 per cent virus suspension inactivated with 0.1 per cent formaldehyde for sixteen hours at incubator temperature.

The children were observed for several weeks for any reaction to the vaccine, and the temperature was recorded four times daily. In no instance was there any local or general reaction. Moreover, the first dose of antigen did not render the children sensitive to the second.

Prior to vaccination the children were bled, and the blood serums were tested for antiviral substance. In each instance from a very small amount to a trace was present. The blood specimens obtained three weeks after immunization showed an appreciable increase in antiviral substance, but whether or not this constitutes a sufficient amount to protect against the natural exposure to the disease must still be determined. However, as the children showed a decidedly better humoral response than did the monkeys, which after similar vaccination became resistant to intracerebral inoculation—a rather severe test—it is likely that the children developed sufficient immunity to resist exposure to the virus. Moreover, after immunization the majority of the 12 children showed what appeared to be a greater antibody content than did 3 children convalescent after paralytic attacks of the disease. Of course, the actual proof will lie in the results obtained following immunization of children on a large scale in an epidemic area in which the incidence of the disease among vaccinated and that among nonvaccinated children under similar conditions of exposure can be compared.

At present several points of practical importance are being investigated. These are: (1) the smallest dose of vaccine that will give an appreciable immunity and its duration and (2) the relative merits of one and two doses of vaccine.

The use of convalescent serum has been advocated in preparalytic cases. This, however, has been practically given up since the controlled results reported by Kramer and Aycock, myself and others. There still remains the possibility that either convalescent serum or serum made by immunizing horses may be used as a preventive in the same way as is measles convalescent serum. I give here a brief statement of work done by Dr. Brebner two years ago. Several attempts to repeat this have been made, but the conditions have not been as favorable.

At present the department of health has a horse serum of high potency and with no antinerve substance. This is obtained either by giving the horses injections of the purified virus or by discontinuing the treatment of immunized horses and not bleeding them for a year or more.

The most interest at the present moment is in the use of a vaccine rather than in the use either of a human convalescent serum or of an antivirus horse serum.

There was unusually little poliomyelitis during the summer and fall of 1932 in New York and its vicinity, but there were outbreaks in some cities in New Jersey and Pennsylvania. Bradford, Pa., was one of these towns, and a large number of children were treated with the blood of their parents and accurate results obtained as to the number of cases of poliomyelitis that developed in the children who were not immunized. Dr. William B. Brebner went to Bradford shortly after the outbreak of the epidemic.

Every opportunity of testing the prophylactic value of adult blood was afforded him by the physicians and by Dr. Vogel, health officer of Bradford. Dr. Brebner reached Bradford shortly after the outbreak of the epidemic (Sept. 10, 1932), when only 8 cases had occurred, and at that time he urged the inoculation of every child under 15 years of age with from 10 to 20 cc. of parental whole blood. The suggestion was acted on, and between September 10 and October 5 about 1,300 children were inoculated. During this period 32 additional cases of poliomyelitis occurred, none of which were among the children who received injections of adult blood.

The injections of parents' blood were begun on September 10, but it was not until September 13 that large numbers of children were immunized. Cases of poliomyelitis developed among those not immunized at intervals throughout the rest of September and the first week of October.

The total population of Bradford is about 18,000; the number of children between the ages of 1 and 15 is probably between 4,000 and 4,500. At first only a portion of the 1,300 children were inoculated with blood, since these inoculations covered a period of twenty-five days, and therefore at the beginning of the test most of the children were uninoculated. In other words, the number of controls decreased throughout the test, while the number of inoculated children increased.

About one half of the total number of the children finally treated had been inoculated at the time of the peak of the epidemic. Nevertheless, the experiment is remarkable in that poliomyelitis did not develop in any treated child. It was thought that modified poliomyelitis would develop in some of the children if they received blood during the period of incubation.

ADULT IMMUNITY TO POLIOMYELITIS AND THE POSSIBLE RÔLE WHICH ATTACKS OF ABORTIVE POLIOMYELITIS PLAY IN ITS DEVELOPMENT. DR. JOHN R. PAUL AND DR. JAMES D. TRASK, New Haven, Conn. (by invitation).

The question implied by the title of this paper has been approached from three angles: 1. What is abortive poliomyelitis? 2. Does it confer immunity to frank poliomyelitis? 3. How common is it?

1. There have been several definitions of abortive poliomyelitis. According to our terminology, frank poliomyelitis represents the form in which in the face of appropriate symptoms the diagnosis rests either on the detection of paralysis or of pleocytosis in the spinal fluid. Abortive poliomyelitis refers to the form which presents clinical evidences of an acute, febrile illness, generally of from thirty-six to seventy-two hours' duration. This illness is usually accompanied by headache and vomiting and occasionally by sore throat and pain in the neck, back or limbs. The diagnosis rests largely on the circumstances under which the case occurs. That is, during an epidemic of poliomyelitis illness of this type should be regarded with considerable suspicion when it arises in families or small communities from which frank cases have also arisen. Further identification of abortive poliomyelitis rests on the fact that the virus of poliomyelitis has been isolated in such cases on several occasions.

2. As to demonstrable evidences of immunity conferred by abortive poliomyelitis, the available methods whereby this may be demonstrated are few. The extent to which the in vitro neutralization test is an adequate measure of immunity to poliomyelitis is unknown. Certainly we do not regard the results of such tests made with old passage strains of the virus as of much significance. Nevertheless, serial tests made with a strain of virus recently isolated from a human being have been performed in 5 of our cases of abortive poliomyelitis. The results, regardless of their interpretation, showed that in 3 of these cases there was a sharp increase of antiviral substance in the sample of blood obtained during convalescence as opposed to the sample obtained prior to or during the early stages of illness. In a fourth case there was a slight increase of antiviral substance, and in a fifth case an antiviral substance was present in samples obtained both before the illness and during convalescence.

3. The ratio of frank to abortive cases has been recently observed in five small communities during the epidemic of poliomyelitis in the New England states in 1931 and in Philadelphia in 1932. In these surveys the abortive cases were found to outnumber the frank cases from four to six times. It seems probable that these ratios would vary in different epidemics. If, for instance, abortion of the disease is an expression of immunity of the host, this variable factor would influence the relative frequency.

In summary, we are confronted by the possibility that poliomyelitis may be a far more common disease during epidemics than has generally been thought to be the case and that paralysis, that is, detectable or residual paralysis, may be only an incidental feature of the disease. The evidence at hand does not prove how or when adults acquire immunity to the frank disease, but it has seemed much more difficult to us to prove that abortive cases do not confer immunity than to show that they do confer some immunity.

AN EXPERIMENTAL APPROACH TO THE PROBLEM OF RESISTANCE IN ACUTE ANTERIOR POLIOMYELITIS. DR. CLAUS W. JUNGEBLUT, New York.

Two opposing theories have been invoked to explain the mechanism of natural resistance to poliomyelitis. The first one, supported mainly by extensive epidemiologic observations, interprets this resistance as the result of immunizing contact with the virus which may take the form of subclinical immunization or of abortive attacks. According to the second theory, poliomyelitis is essentially a developmental disorder of juvenile age and protection against the disease chiefly a function of the normal endocrine balance.

The experimental facts favoring the theory of maturation may briefly be summarized as follows: 1. The frequency of neutralization of the virus by serums from persons known to have experienced contact with the virus (convalescent serums) is no greater than that observed with serums from persons whose contact with it is only assumed (normal serums). 2. The virucidal titer of serums of convalescent patients, blood group for blood group, is not appreciably higher than that of normal persons. 3. The percentage of normal serums that neutralize in localities with varying incidence of epidemic poliomyelitis is inversely proportional to the known clinical manifestations of the disease among the respective populations. 4. The poliomyeliticidal substance in human serum, normal and convalescent, differs in immunologic characteristics from the neutralizing substances in antibacterial and other antiviral serums in that it is not specifically absorbable and fails to give such fundamental immune reactions as alexin fixation and precipitation or flocculation. The specificity of the inactivation of the virus of poliomyelitis by serum is questionable, since marked cross-reactions occur with certain antitoxic serums (antidiphtheritic, antiscarlatinal and antisnake venom). 5. Poliomyeliticidal substances are found in man and in animals in sources which are rich in anterior pituitary hormone (placenta and urine of pregnant women and serum of pregnant mares). Adrenal cortical and medullary hormones are capable of inactivating the virus of poliomyelitis directly in vitro. 6. Poliomyeliticidal substances have been produced in the serum of rhesus monkeys after preparation with anterior pituitary extracts and anterior pituitary-like principles. 7. Bilateral adrenalectomy is followed by a disappearance of the poliomyeliticidal substance in the serum of normal Nicaraguan cebus monkeys, while the same operation, as a rule, has no effect on the presence of such substances in the serum of convalescent or artificially immunized rhesus monkeys. 8. Examination of the endocrine system of children dying of poliomyelitis demonstrates a consistently larger weight of the thymus. The adrenals of poliomyelitic monkeys show hemorrhages as well as cellular changes which indicate an acute demand on the organ. 9. There is some clinical evidence, even though debatable at the moment, that children attacked by poliomyelitis present certain constitutional stigmas which are referable to dysfunction of the anterior lobe of the pituitary gland and the adrenals. 10. Statistical analysis of the figures on morbidity and mortality in cases of poliomyelitis reveals the presence of a second pubertal wave and a shift in the sex distribution after the development of puberty.

11. The seasonal incidence of poliomyelitis coincides with cyclic fluctuations in the operation of certain internal secretions. It also compares closely with that of a well known deficiency disease, beriberi. 12. The importance of a possible genetic factor as affecting individual resistance is suggested by the characteristic pattern of blood group distribution in children with poliomyelitis.

The facts cited suggest the operation of a marked constitutional factor in the development of poliomyelitis. In the absence of evidence proving individual variations in immunizability according to blood group, age, race, climate and season, it is concluded that this constitutional factor is the primary agency controlling resistance or susceptibility to the disease.

DISCUSSION OF PAPERS ON ACUTE ANTERIOR POLIOMYELITIS

DR. JOHN L. RICE: From the number of years that I have been in administrative public health work I think that one of the most difficult tasks any officer faces is deciding what to do in the face of an outbreak of poliomyelitis. The public demands much. All one can do is to apply symptomatic treatment. There is difficulty in knowing what is the right thing to do. Swimming pools are closed. Schools are closed. Many other things are undertaken, but I have not, up to the present, found any solid basis for administrative public health control work in cases of poliomyelitis. During the past six months the New York department of health has attempted to set up a general program for use in the event of an outbreak.

The first time that I attended a meeting on poliomyelitis was in Washington, in 1912, at the International Conference on Hygiene. Dr. Rosenau proposed the theory that the biting fly is the causative agent of poliomyelitis. From that time on innumerable studies of this problem have been made and published, but up to the present nothing of outstanding value from the standpoint of help to the health officer has been advanced. It looks now, however, as if the pieces of the puzzle are beginning to fit together and that in the future, there will be some definite information that will help public health administrators to control and to eliminate this disease.

DR. JOSEPHINE NEAL: I shall limit my discussion to a consideration of the relationship of these papers to treatment. Dr. Brodie stated, and I wish to emphasize, that experimental work bears out the clinical results which were obtained in the epidemic of 1931, when the results in a large group of patients whose cases were diagnosed in the preparalytic stage and who were treated with serum were compared with the results in a practically similar number of patients whose cases were diagnosed in the preparalytic stage but who did not receive serum. In spite of the fact that the results in the two groups were practically the same and that any slight difference was in favor of the group of patients who were not given serum, nevertheless, there are present many physicians who continue to advise the use of serum when they see an early case of poliomyelitis. I am glad, therefore, to have the scientific proof added to the clinical proof, for certainly if the serum is of no value the giving of it in the treatment of the disease is not the best procedure.

This work on the pathogenesis of poliomyelitis also brings up the question of the possible value of forced spinal drainage, which has been recommended of late as a method of therapy. If the virus becomes attached, and so early attached, to the nerve cells, it certainly does not seem that it can be removed by any mechanical means such as forced spinal drainage. Therefore, it seems that those who have advocated this in cases of infantile paralysis should first show experimentally (1) that it is possible to remove the virus by forced spinal drainage in the experimental disease and (2) that animals with experimental poliomyelitis do better when they have received forced spinal drainage. This same line of argument applies also to the use intraspinally of drugs such as ephedrine sulphate and similar preparations, which were advocated long ago and which I remember were used in 1916 and again advocated in 1931. If the lesion is essentially one of direct injury to the cell by the virus, the action of such drugs can do no possible good. Treatment that has no definite indication should certainly be eliminated.

DR. FREDERICK TILNEY: In 1916 I served as secretary of the commission appointed by the New York Academy of Medicine and the New York Neurological Society to investigate the epidemic raging in the city and throughout the country at that time. The matter was studied for many months, and as I have listened to these valuable contributions I have been wondering how much substantial progress and advance have been made in those eighteen years in this matter of poliomyelitis, with reference either to its treatment or to a better understanding of its nature.

Referring to the portal of entry of the virus the members of the commission thought at that time that there was sufficient evidence to believe that the nasopharynx was that portal. They even offered the rather naive suggestion to parents to avoid gargles and nose sprays lest what natural protection there might be in the mucous membranes would be injured. I think, however, that while Dr. Brodie brought out rather important evidence bearing on the fact that the fila olfactoria are the probable means of conduction of the virus into the central nervous system, one must have certain reservations and caution in accepting that as final. In the first place, how is it that so few symptoms appear in the midbrain and in the hemispheres, in what Dr. Brodie has chosen to speak of as the rhinencephalon, and that the virus immediately makes its way down to the lowest segments, as remote as possible from the olfactory bulb, the spinal centers, where it has its greatest effect? I am not at all convinced that the so-called English school, led by Hurst and Fairbrother, is correct in contending that the virus is conducted from this portal of entry by the nerve tracts. If so, there are tracts which I know nothing about which serve for this conduction, because the natural routes of conduction by the nerve fibers from the rhinencephalon are limited, and hardly any of these tracts reaches as far down as the upper part of the cervical portion of the cord. Dr. Brodie's suggestion as to the antiviral action of the hemispheres and stem is an excellent one, but it certainly needs further investigation.

I remember also that the members of the commission debated long about the matter of abortive cases supplying immunity, and the upshot of the debate was apparently much as it is today. The decision as to the selection of criteria for determining the abortive cases is still doubtful. It seems to me that the one great advance that has been made in the past eighteen years is the convergence on this subject of so much effective research work, and while that research work has perhaps not yet borne fruit that will serve the purpose in the immediate present, I think that it gives great promise and one can expect a great deal from it. That further advance has not been made should not discourage one, although I consider the situation an open challenge.

DR. BERNARD SACHS: I was associated with Dr. Tilney in 1916, and I believe even in 1912 I was intimately concerned with the question of poliomyelitis. This morning I looked up what I said about poliomyelitis in the first edition of my book, "The Nervous Diseases of Children," published in 1895 and written at least in 1894, exactly forty years ago. It was rather surprising to me as I read it over to find that in 1894 I said, and evidently I was not the first one to say it, that poliomyelitis was an infectious disease and that it was likely to affect several members of a family; and what surprised me more was that I said that in all probability the same infection that caused poliomyelitis might possibly cause an epidemic, or something like an epidemic, of encephalitis. During the past forty years—and that is going back further than Dr. Tilney did—neurologists have been intimately concerned with the question of poliomyelitis. Much progress has been made, particularly as to the pathogenesis of the disease, but I also think that by no means has any definite conclusion been reached regarding several of the important questions.

I was much impressed by what Dr. Brodie said about the fact that the virus travels along the olfactory bulb and nerve, but I doubt whether that is the only portal of entry or the only course the virus travels. Even the block experiment and the fact that the spinal cord was cut does not impress me much. Cutting through a nerve opens any number of other tracts by which the virus might travel. The fact that the virus is found in the nerve cell does not to my mind prove that it travels along the nerve. It is pretty well established now, for instance, that the

spirochete of syphilis is actually found in the cells of the cortex, but one would not claim for that reason that the spirochete travels by way of the nerve tissue. I have no doubt that the lymph spaces—and I am not yet willing to deny the blood circulation—may play an important part in carrying the virus into the central nervous system.

Whether the nasal orifice is the only portal of entry is another question that has been in my mind, although I have not much faith in the gastro-intestinal tract as a portal of entry. I think that it is well to bear clinical facts in mind. For many years I was in charge of a neurologic ward, and before there was much concern about poliomyelitis as an epidemic disease all the patients with neurologic conditions were kept in the general wards of the hospital. I cannot recall a single case of poliomyelitis that appeared to arise as a result of direct contagion from another patient in the ward. Those are very important facts. If the nasal orifice is the only portal of entrance it seems to me remarkable that there were not more cases in which the contagion was carried from one person to another, even allowing for the immunity of many persons.

There is another reason that the neurologist and the clinician should work in close accord with the bacteriologist and the research worker, and that is that there is the greatest possible danger in all these statistics regarding abortive cases. The abortive cases are perhaps easy enough to recognize during the time of an epidemic because almost anything that looks like an acute infectious disease in a family in which there is a case of poliomyelitis will in all probability be put down as an abortive case of poliomyelitis. Whether lumbar puncture will prove the nature of the condition is, I think, still in doubt with clinicians. I have no doubt that abortive cases do occur, but all the diagnoses that are made of poliomyelitis of the abortive type, or even of the preparalytic stage, to my mind must be carefully considered before any inferences or conclusions are drawn from them.

I am glad to hear and to support Dr. Neal's opinion regarding forced spinal drainage. There seems to me to be good evidence to believe that it is more or less unnecessary, and as it is also a serious procedure I think that it would be well, until there is definite evidence as to the good it does, to abandon the idea of forced spinal drainage as a therapeutic measure.

DR. GEORGE DRAPER: Dr. Brodie's contentions were exceedingly clearly put, but I wish to ask one or two questions. If it is true that the virus becomes fixed to the nerve tissue and therefore is not accessible to serum, how does it happen that immune bodies develop in the blood?

One can assume that in any given epidemic, no matter what its violence—and this may vary from the extreme degree of the epidemic of 1916 to that milder expression which has recently been observed in Los Angeles—the virus is ubiquitous. Yet there is an immense variation in the severity of individual cases. The range extends on the one hand from the carrier, who with complete resistance goes about unrecognized, to the person who is crippled or whose case is fatal. But these widely differing effects are produced by the same virus. There must be another factor not yet disclosed which explains the phenomenon. In that connection Dr. Brodie remarked that the tissue of the brain had a different action on the virus from that of the tissue of the cord. At least there is a demonstration that within the body there are certain components of its constitution which have a different reaction to the virus. Now, the trend of modern biology is in the direction of the belief that the whole is greater than its parts. This is known as the organismal as opposed to the elementalist point of view. In application to the problems presented by patients one might speak clumsily perhaps of "clinical organismalism." If a difference exists between the brain and the spinal cord, one is justified in looking for a difference in the reaction of total organisms to the virus. This is demonstrated in the extreme difference in the reaction of the carrier on the one hand and of the person with a fatal case on the other.

As far as Dr. Paul's remarks on abortive cases are concerned, it seems to me that the classification is most confusing and has blocked a clear vision of the disease for a long time. The fact that the virus moves continuously through the central nervous system makes one consider that perhaps the whole disease picture

should be viewed as a continuous process and that the character or flavor of a given case is determined by two factors: (1) the severity of the case, which is determined by the relation between the virus and the given patient's resistance, and (2) the stage at which the advance of the virus is arrested. That gives the character to the individual case: the severity and the point at which the advance of the virus ceases.

Dr. Park spoke of the antinerve quality in the horse serum which was prepared at one time and of the distinct variation in the irritating effect which that serum had on different subjects. It is curious that that same serum produced a definite reaction in one person and not in another. This discrepancy could not have been due to the serum alone. It seems that differences in the individual human recipients must play some part.

That brings me to Dr. Jungeblut's paper, which dealt with the disease from an entirely different point of view. Up to now the immunologic point of view has been considered, always from the side of the attacking agent. Little has been said about the resisting agent, which shows about as great a degree of variability as does the virulence of the virus. There has recently come from the laboratories of Prof. Heinrich Pol, formerly of Hamburg, a paper on poliomyelitis showing the same findings as those obtained by Dr. Jungeblut and others concerning blood groups and also the most astonishing observations on finger-prints. The paper states that the poliomyelitis types have been determined by means of finger-prints. So far as the genetic story is concerned, a great deal of work has been done on that, and a good many excellent clinical observations have been made. In 1923, for example, DuBois in Zurich studied 310 families. In those families he found a high number of collaterals and direct lineal descendants who had had the disease. He also had three sets of identical twins. In two sets of these both members had the same disease at the same time, and in one set both had the same muscles involved. In the third set only one twin had the definite disease, but it is not stated whether some slight transient indisposition went unreported in the other. Any one who has worked actively in an epidemic of poliomyelitis must have seen families in which multiple cases occurred. I remember one family in which 5 children were infected at the same time. That was the group that started a search for the constitutional element. The patients gave the impression of a litter of guinea-pigs, they were so similar in appearance.

I will not discuss the type at this time, but I believe that the persons who contract poliomyelitis are recognizable and form a specific type. A specific human type is just as essential to the development of poliomyelitis as is a specific virus. If this is true, then in the severer cases in a given epidemic, in which the virus can be assumed to be similar, the specific human type is the more significant factor.

When I heard that Dr. Jungeblut was doing laboratory work on poliomyelitis I asked him what he was doing. He said that he was using some glandular extracts. It is interesting that he was working with extracts of the three glands which I had suspected were deficient in children with poliomyelitis—the anterior lobe of the pituitary, the gonads and the adrenals. It is curious that the adrenals have come to be suspected, and it is also striking that children with poliomyelitis show a very high percentage of pigmented moles. In many cases I have seen well defined vitiligo.

Therefore, I would say to the proponents solely of the theory of infection and immunity on a specific basis: Why is there this great range in severity, when the virus is ubiquitous, between the carrier and the person with a fatal case? Why, if the virus is fixed and cannot be approached by the serum from the outside, can it produce antibodies in the blood? It seems that one is being forced by the curious phenomena of this disease to go further into the question of non-specific immunity. At the moment one cannot discard the consideration of forces which shift and change in the process of growth and development.

Dr. S. D. Kramer: Recent experimental and other studies have served to establish the epidemiology of poliomyelitis on a firm basis. It may be well to review the results of some of these studies and to draw attention to the similarity of this disease to better known and more common diseases, such as diphtheria and measles.

These studies have indicated the contagious nature of poliomyelitis. The recovery of the virus from nasal secretions of persons with the disease and of those who have come in contact with it and the ease of infecting the experimental animal by nasal instillation of the virus have suggested its mode of entrance and the means by which it may be spread. The extensive immunity among the normal urban population to this rare disease strongly suggests the presence of healthy carriers, as has been proved for diphtheria.

Greater knowledge of the disease has contributed little, however, toward its control. The more recent experiments with convalescent serum as a therapeutic or prophylactic agent have proved to be failures or have given inconclusive results. More hopeful have been the efforts for devising some method of vaccinating against the disease. To the critics of such efforts one might point out that the rareness of the disease is considerably neutralized by the extraordinary terror of a community visited by an outbreak. Furthermore, it should be remembered that since one is dealing with a disease affecting primarily the childhood population (about 65 per cent of the cases occurring in children under 5 years) the incidence of the disease takes on greater proportions and significance, and it seems reasonable to suggest that until some means for identifying susceptible persons is devised some method for active immunization should be developed.

A word of caution must, however, be voiced concerning any method devised to vaccinate against poliomyelitis. When compared with measles and diphtheria, poliomyelitis remains a rare disease, and for that reason more than usual caution must be exercised to assure the safety of the method employed, because the occasional accident will approach or may even exceed the incidence of the disease. In spite of the expense involved in experiments with poliomyelitis, considerable and extensive evidence must be presented before any method can be recommended for trial on human beings. Volunteers who are willing to be inoculated are, of course, to be commended, but their significance must not be overestimated and should be cautiously evaluated, for until a significant number of experiments are conducted proper evaluation is not possible.

Another factor which may point toward caution and further experimentation is suggested by work recently published that indicates the existence of immunologic and qualitative differences in different strains of the virus of poliomyelitis. A few years ago Burnet and Macnamara reported some differences they observed in a strain of virus isolated by them locally, in Australia, from the laboratory strain with which they had been working and which originally came from the United States. Later that same year Weyer reported similar differences between a strain isolated recently in New York and the laboratory strain with which he had been working. A year ago Paul and Trask studied a number of strains from different sources; one of these strains they had isolated in a fatal case in New Haven; a second strain had been isolated recently in a fatal case in New York and the third strain was an old laboratory strain. These authors observed differences similar to those observed by Burnet and Macnamara and by Weyer.

During the past year the immunologic properties of specimens of the Australian and New Haven strains of virus have been studied in the laboratories of the Infantile Paralysis Commission of the Long Island College of Medicine and have been compared with several laboratory strains. Because of difficulties usually encountered in establishing a human strain in the laboratory animal and because of certain differences in the resulting experimental infection between recent and old strains, the members of the commission have been loath to accept the reported differences as evidence of basic immunologic differences. A study of the serums of a series of animals immunized against these different strains has, however, tended to confirm the earlier observations. The clearcut results of the compiled protocol to be given advances more definite evidence of what appears to be basic and qualitative immunologic differences between these strains. (The plus sign indicates that the virus is neutralized and the minus sign that it failed to become neutralized.)

Virus Strain	Laboratory	New Haven	Australian
Laboratory	+	—	—
New Haven	—	+	—
Australian	—	—	+

Should further experimentation establish the existence of multiple strains, any vaccine, to be generally effective, will have to include them all as they are identified. It may furthermore necessitate a revaluation of earlier results with convalescent serum, both therapeutic and prophylactic.

DR. MAURICE BRODIE: Dr. Draper asked how, if the virus is entirely localized to the central nervous system, do immune bodies appear? I believe that the immunity is developed not in the central nervous system, but outside, for in work on poliomyelitis and other virus diseases it has been impossible to immunize animals by intracerebral inoculation. Likewise, if the olfactory nerves are cut in animals, they can be immunized. The immunity is developed outside the central nervous system. Histologic studies show that these destroyed nerve cells are carried away by microglia cells, and they probably take the virus to the perivascular spaces and thence to the blood vessels. It is then carried by the blood system to other organs like the spleen and liver and sets up immunity there.

In reference to the damage produced in cutting the olfactory nerves, the only damage is to these nerves. The fifth and seventh nerves are not damaged. In reference to the gastro-intestinal tract and other portals of entry, if the olfactory nerves are cut the virus can be introduced and the animals are still not infected.

PHILADELPHIA PSYCHIATRIC SOCIETY

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JOSEPH C. YASKIN, M.D., *President, in the Chair*

MULTIPLE FOREIGN BODIES IN THE GASTRO-INTESTINAL TRACT: REPORT OF A CASE. DR. JAMES GREENWOOD JR. (by invitation).

The intentional ingestion of foreign bodies is a not infrequent and dramatic complication of mental diseases, and it occurs frequently enough that the condition must be thought of whenever unexplained gastro-intestinal symptoms arise suddenly in a psychotic patient. The diagnosis is often made difficult by the fact that no history is obtainable, and the first symptoms suggest some acute inflammatory abdominal lesion or intestinal obstruction, or both. Many patients with this condition have been treated at the Philadelphia General Hospital, one of the most unusual cases being that of a young man suffering with dementia praecox who died in 1909 of peritonitis thought to be secondary to a ruptured appendix. At necropsy sixty-five articles were recovered from the region of the cecum, including needles, nails, safety-pins, wires, buttons, stones, a can-opener, a key and a locket.

During the past year 6 mentally ill patients with foreign bodies in the gastro-intestinal tract were admitted to the Philadelphia General Hospital.

The first patient, a young man with schizophrenia, with good insight and periods of depression, swallowed a teaspoon, supposedly with suicidal intent. Owing to severe gastro-intestinal symptoms, gastrotomy was performed, and the article was successfully removed.

The second patient, a mentally defective boy with parkinsonism, swallowed an open and a closed safety-pin. At operation the open pin was successfully removed from the stomach, but the other pin was not recovered.

The third patient, a mentally defective girl, was admitted from the Philadelphia Hospital for Mental Diseases suffering with acute gastro-intestinal symptoms. At operation, twenty-four lead pencils were removed from the stomach. This was the patient's second operation for the same condition.

The fourth patient, an imbecile with congenital spastic diplegia, swallowed an open safety-pin. The pin was removed from the stomach, but the child died several days later of pneumonia.

The fifth patient, a man with rather marked depression, swallowed a half-dollar, which was removed from the stomach by surgical means. Soon after the

operation he appeared so much improved that the coin was given to him as a souvenir. Several days later he swallowed it again and was allowed to keep it.

There is no great number of these reports in the literature in spite of the frequency of the condition in patients with mental disease. There are few references to the type of patient who is most likely to swallow foreign bodies or statements concerning the motivating force, but most of them are assumed to be suicidal attempts. The greatest number of objects found in any one of the recorded cases was 2,533 (*Arch. Surg.* **16**:494 [Feb.] 1926). The heaviest article weighed 5 pounds and 3 ounces (2,353 Gm.). Objects of various sizes, such as knives, forks, spoons and similar objects, have been swallowed.

The history in these cases is often unreliable, and the diagnosis depends on roentgen examinations or on laparotomy. The treatment of choice is first medical, then surgical, since many foreign bodies are passed spontaneously. A patient who had swallowed a 50 cent piece and a large open safety-pin was given ¼ pound (113 Gm.) of butter and ¼ pound of absorbent cotton. The bodies were passed spontaneously without harming the patient (*M. Bull. Vet. Admin.* **7**:50 [Jan.] 1931). When, however, the bodies are not passed and gastro-intestinal symptoms develop, particularly those of inflammation or obstruction, surgical intervention is indicated.

Report of a Case.—H. B., a Negro aged 45, was admitted to the medical department of the Philadelphia General Hospital on July 18, 1934, complaining of epigastric pain, vomiting and hematemesis which had occurred on three occasions. He gave the history that he had not felt well for several years and had had vague abdominal pains. Two months prior to admission he began to have severe pain in the upper portion of the abdomen occurring daily but having no relation to the ingestion of food. At times the pain was cramplike, and its severity would cause him to double up. One week previously he had vomited bright red blood. There was no history of tarry stools. The remainder of the history was essentially unimportant. He had worked all of his life at heavy jobs, usually loading and unloading trucks. In the remote past he had been a free user of alcohol.

Physical examination gave entirely negative results except for some hyperperistalsis. Peptic ulcer, cirrhosis of the liver and a gastric malignant condition were considered diagnostic possibilities. A roentgenographic study of the gastro-intestinal tract revealed a large clump of nails near the pylorus and other nails in the ileum and cecum. A more careful examination of the abdomen revealed a definite mass in the region of the epigastrium.

The patient denied all knowledge of how the nails could have entered his gastro-intestinal tract, but he admitted that he had worked as a carpenter's helper for several weeks preceding admission to the hospital. Up to this time a psychosis had not been suspected, as he had been quiet, well behaved and cooperative. However, he was transferred to the psychopathic department. Preliminary mental examination there revealed no definite psychotic symptoms, but it was soon discovered that he was of much lower intelligence than had been suspected. He was unable to add or subtract the most simple sums. He had served in the army during the World War, but he said that he was not sure who the enemy was unless it was Japan. He could read only a few elementary words in spite of having gone to school for several years. He was well oriented for time and place. He continued to deny knowledge of having swallowed the nails but after prolonged questioning stated that he could get rid of them himself. Then he volunteered the information that Jesus was in his stomach and made reference to the crucifixion with nails and to his father and brother lying in coffins with nails. He then pointed to the roentgenographic report which spoke of the nails in his abdomen and said "That is a coffin" and that he would be able to "enjoy life forever by taking the nails for the sake of Jesus." Except for these remarks, made confidentially, he would say nothing more and usually refused to discuss the matter. He was cooperative in other ways but was a little evasive and slightly euphoric and sometimes assumed a fixed smile. At no time would he look directly at the examiner. The provisional diagnosis was psychosis with mental deficiency and self-administered foreign bodies in the gastro-intestinal tract.

By August 20 the patient had passed between twenty-five and thirty nails, and a roentgenographic examination showed only four remaining, two in the right lower quadrant and two in the rectum. On this date there developed a severe cramplike pain in the middle of the abdomen, and the patient was transferred to the surgical department for operation, but as the pain subsided it was decided to postpone the operation. He was returned to the psychopathic ward. Subsequently the remainng nails were passed spontaneously.

A gastric analysis revealed no free hydrochloric acid and the total acidity was somewhat lower than normal, varying from 8 to 37. No blood was found in the gastric contents, but occult blood was reported in the feces. The Kahn reaction of the blood was doubtfully positive, and the Wassermann reaction was 1 plus with cholesterolized antigen but negative with the Noguchi antigen. The Wassermann reaction of the spinal fluid was negative; the colloidal gold curve was 0011100000. The red blood cells numbered 3,210,000 and the white cells, 5,500; the hemoglobin was 75 per cent.

The patient was committed to the Philadelphia Hospital for Mental Diseases on October 4.

Conclusion.—In the light of our experience it appears that most cases of ingestion of foreign bodies in psychotic persons occur in three types of patients: those mentally defective, those with depressions, with suicidal intent, and schizophrenic patients whose motive is probably a symbolic one.

DISCUSSION

DR. CHARLES W. BURR: I am sure that the motive for swallowing the nails was a compulsion. This man had religious delusions in a way no normal man could understand. He connected the Lord with the nails in his stomach. Heaven was a place to reason about, and he believed that it was to his spiritual advantage to swallow nails. It is natural to jump at the conclusion of suicide. I once made a positive error by doing that. A woman told me that she wanted me to take care of her husband who had swallowed an unopened penknife. I foolishly permitted her to influence me. She said that he had been depressed. When I asked him why he swallowed the knife he remained mute. As it turned out, it was not a suicidal attempt at all. He had a religious delusion. He believed in some mystical way that the knife stood for something and if he swallowed it the Holy Ghost, who wanted him to do it, would see that he benefited by it. He swallowed many things, all suddenly. He acted on impulse.

DR. WILLIAM L. LONG: I shall mention 1 case in which I was at first sure that the patient was trying to commit suicide. She escaped from the nurse, broke a milk bottle and ate the glass. Afterward she told me that she thought that if she got out of bed she would fall apart, and she swallowed the glass so she would have to stay in bed.

DR. L. H. SMITH: There was a similar case at the Pennsylvania Hospital a few years ago. A patient with suicidal intent swallowed a toothbrush which lodged in the stomach, bristles up, with the handle passing through the pyloric opening. Dr. Farr immediately tested a number of different types of toothbrushes in hydrochloric acid of various degrees of concentration. By this means it was found that the type of toothbrush in the stomach would digest slowly, and it did digest through at the narrow neck. Both the handle and the bristle ends were passed in a few days. From then on the hospital used digestible toothbrushes! Another case was that of a feebleminded man who swallowed five large safety-pins after opening them. These safety-pins were followed through the gastrointestinal tract by roentgenographic study, and in a few days all had been passed.

DR. R. A. MATTHEWS: The defective girl who swallowed the pencils recently swallowed a good-sized teaspoon, which was passed spontaneously. At various times this patient has swallowed closed safety-pins, bobbette pins, straight pins and victrola needles. She swallows these objects not with suicidal intent but merely to gain attention. The mentally defective boy with parkinsonism was definitely depressed and had suicidal intentions. His sister had recently died in status epilepticus and his father ceased visiting him, so he thought that he would never

get out of the hospital. The other boy, with congenital spastic diplegia, had fits of depression when he would tell me that he wanted to die. He would say, "I think I am going to do something to myself," and would ask to be put in restraint. His mother had promised to take him home for a few days but failed to keep her promise. He retaliated by swallowing the open safety-pin. However, I do not believe it was a frank suicidal attempt.

DR. J. GREENWOOD: I purposely omitted the reasons why these patients swallowed the foreign bodies. I do not know enough about it myself, although I think that in cases of dementia praecox it is symbolic. Dr. Matthews has cast some light on the mechanism in cases of mental deficiency, and in certain other cases the objects are swallowed with suicidal intent.

EPILEPSY AND ARTERIOSCLEROSIS. DR. ALFRED GORDON.

I have tried to envisage epileptic phenomena as manifestations of a progressive material damage to the motor cortex produced by progressive sclerotic changes in the cerebral blood vessels. Within the last ten years a large number of brains from persons with arteriosclerosis have been examined; the histories of some of the patients contained descriptions of typical epileptic seizures which made their first appearance at an advanced age. In 12 of a series of 75 persons who died of various visceral causes, death occurred suddenly or rapidly after apoplectic insults. Besides hemorrhagic or thrombotic foci which could explain the immediate cause of death, there were a multiplicity of yellowish spots over the cortex, with predominance over the motor areas, and some minute adhesive areas, as evidenced by attempts to peal off the pia-arachnoid membrane. Small fragments from some of these pathologic areas were examined histologically, and cellular changes with regard to the shape, size and nucleus were distinctly present. Although these gross and microscopic lesions were present in a diffused manner, from one pole of the cerebrum to the other, the predominant number of foci of involvement were seen over both motor areas.

In analyzing the clinical histories in the 12 cases, there were the usual manifestations of arteriosclerosis, namely, hypertension, headache and particularly vertiginous attacks. As to the convulsive seizures themselves, nothing was wanting in the picture observed in cases of epilepsy of any other origin. Sudden onset with unconsciousness and violent muscular contractions on one or both sides, followed by unconsciousness, were all present.

In an attempt to correlate the anatomicopathologic changes with the attacks of epileptic seizures one must admit that the isolated epileptic crises are due either to temporary circulatory disorders in the form of ischemia, produced by arterial spasm, so common in cases of arteriosclerosis, or to a sudden inflammatory exacerbation in the small areas of chronic meningo-encephalitis which I found to be so abundantly distributed in the entire series of 12 brains. The pathologic lesions observed in my cases were of a disseminated distribution. They were found over the occipital, frontal and temporal lobes, as well as over the motor area.

The conclusion to which the cases lead is that a lesion of any portion of the brain may be accompanied by epileptic seizures and therefore may be considered as an epileptogenic zone. Irritation, inflammation or damage of any portion of the intracranial contents, whether it is over the vertex of the cerebrum or the cerebellum, at their base or in their interior, is likely to produce convulsive seizures with the same characteristic features as those in cases in which there is a distinct lesion in the cortical motor area. Transmission of irritation to the motor cortex is a sine qua non in cases of epilepsy, and this transmission occurs through the association fibers and commissural and projective tracts which connect the motor cortex with various regions of the brain. However, a more critical analysis of the histories of persons with generalized arteriosclerosis forces me to admit that cerebral arteriosclerosis, in which pronounced mental disturbances are present and are due to this arterial disorder, may not lead to epilepsy. There are cases of arteriosclerosis in which large areas of softening are observed post mortem and in which during life gross symptoms of cerebral damage, such as hemiplegia, aphasia, etc., were present and still the condition was not accompanied by epilepsy. On the

other hand, in 4 of the 12 cases mentioned the same macroscopic and microscopic pictures were present and there were no epileptic manifestations during life. While one cannot escape from giving weighty consideration to the pathologic changes in the brain, which were apparently due to the sclerotic changes in the cerebral blood vessels, one must admit that there must have been still another causative element in the epileptic manifestations. Was it a morbid predisposition or heredity? As to the hereditary predisposition, the consensus is in favor of such an influence. Epilepsy and psychoses in relatives are not infrequent in the medical antecedents of epileptic patients. Heredity in all such cases presumably creates a functional exaggeration of the dynamism of the nervous system which in the presence of some organic lesions will be transformed into epilepsy. Hereditary predisposition usually becomes manifest in infancy or in adolescence. Predisposition may remain latent for many years until some break in cerebral equilibrium takes place, such as acute or chronic intoxication (alcoholism, saturnism or paludism) or syphilitic infection, or when some organic disease of the brain (tumor, etc.) supervenes. All these factors create a profound disorganization of the cerebral equilibrium. The latter leads to progressive development of mental deterioration or, as in my cases, to epileptic seizures. Whatever part these circumstances had in provoking the attacks of epilepsy, the unalterable fact remains that minute anatomic and histologic lesions were found widely distributed over the cortex, which were intimately associated with sclerotic alterations of the blood vessels of persons of advanced age. One cannot escape from the position of an organic substratum of epilepsy in cases of cerebral arteriosclerosis. One is reminded of the postulate of Lasègue enunciated many years ago: "Epilepsy which makes its first appearance after the age of 18, should be considered as due to a lesion in the encephalon."

A Case of Speech Defect. Dr. Gerald H. J. Pearson.

A boy aged 5 showed a speech defect of the nature of word mutilation with elision of the initial consonants, so that his speech was extremely difficult to understand. He showed also a masochistic personality reaction and numerous masochistic fantasies; these fantasies occurred in connection with the traumatic situations of his life, i. e., bladder training and the primal scene. The history of the speech defect was that, following a severe injury to the tongue at 18 months (when he had started to speak), he stopped talking for a year and then resumed with a speech defect. The case raised the question of the association of the masochistic fantasies and the speech defect, and it seemed from the material he produced that the trauma to the tongue, occurring as it did just at the end of the second oral phase, destroyed an avenue for the expression of oral aggression. As a result, the aggression, instead of being directed externally, was directed internally to produce a masochistic reaction, and each succeeding trauma increased the masochism. This masochistic reaction was lessened during treatment, and complete improvement occurred in the speech defect with an outburst of violent oral aggression. The diagnosis was traumatic neurosis.

Dr. F. H. Allen: Dr. Pearson is to be congratulated for presenting a paper which is based on the actual treatment of a patient. This child's speech difficulty seemed to act as a symbol of withdrawal from relations with other people. From the material one can see that he had a great deal of aggression which he was unable to handle in a healthy and open way. The speech difficulty helped him to withdraw from the reality of actual contacts with other people, and also helped him to disguise the amount of aggressive feeling that he had. In the early part of treatment he withdrew himself and fought against any kind of relationship with the therapeutist. It took many interviews before Dr. Pearson was included in his interviews, which meant that the child was beginning to accept him as a person. As this relationship progressed the child was able to experience more feeling in direct terms; as this process went on there was less need for the continuation of the speech difficulty, because the child was reaching the point where he could handle his feeling more in the open. The case is an interesting illustration of the therapeutic value that a relationship can provide to a child with this type of difficulty, aside from the reliving and reexperiencing of original events.

Unfortunately, a large number of persons with speech defects do not progress so satisfactorily. The mere fact that the turmoil is so great that it requires the substitution of a symptom, like a speech difficulty, renders the person rather inaccessible to treatment. I have in mind a child, aged 9 years who stutters very severely on occasion; when this child comes close to any feeling in his relation to me, he either stutters much worse or withdraws completely into silence. First he uses speech as a way of protecting himself from experiencing any feeling, or if the feeling is too great, speech drops out entirely. The difficulty in establishing a therapeutic relationship in these cases is great.

Dr. William L. Long: I wish to ask about the tendency of the patient to fall and hit himself. I should think that if the child were nonagressive it would be the other way about.

Dr. J. C. Yaskin: The speech defect in this case consisted in word mutilation, with elision of the initial consonants. Clinically this sort of speech defect differs from stuttering. The latter is often a compulsion type of neurosis, resembling the multiple tics of later life in which therapeutic results are unsatisfactory by any method of treatment. The speech defect in Dr. Pearson's case is comparable to the hysterical types of the adult, and clinically it is generally known that in these cases recovery occurs spontaneously before the age of 10. This statement is not intended to detract from the value of the excellent presentation and the lucidity of the material presented.

Dr. G. H. J. Pearson: I am glad that Dr. Yaskin brought out the point that this case differs from the ordinary case of speech defect, such as stuttering, in that it is not a compulsion neurosis. In my opinion the diagnosis is traumatic neurosis following an injury of the tongue which interfered with the boy's oral aggression. The aggression became dammed up within him and consequently became dangerous, and to me the behavior was a protection against his own oral aggression. I was surprised when this child recovered, because my experience agrees with that of Dr. Yaskin that the ordinary compulsion neurosis with stammering is extremely difficult to treat. There has been a complete change in the boy's personality since treatment was completed. His play at the present time is that of a normal boy of his age. There is no question of lack of intelligence, as his intelligence quotient is 106.

I presented this case because of the masochistic reaction to every traumatic experience in this boy, which would tend to call forth his aggression. Every time he actually became angry he would hurt himself by falling, hurting himself, etc. This reaction became much less during treatment, and at the present time he seems to be behaving normally.

Can We Formulate the Problem of the Neuroses More Concisely? Dr. O. Spurgeon English.

This article will be published in full in a later issue of the Archives.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Oct. 18, 1934

Theodore T. Stone, M.D., *President, in the Chair*

Congenital Dermal Sinuses: A Source of Meningeal Infection. Dr. Paul C. Bucy and Dr. A. Earl Walker.

The histories of 2 cases were presented in which a hairy dimple had been present in the midline of the back from birth. In one case the dimple was in the upper portion of the thoracic region, and in the other, in the lumbar portion. Both children, one at the age of 6 months and the other at 2 years, had suffered from

a severe illness which was diagnosed as tuberculous meningitis, but from which they recovered. Subsequently at 5 and 3 years, respectively, marked weakness of the legs developed, which was spastic in one case and flaccid in the other. In the first case lumbar puncture revealed a yellow fluid with a partial block of the subarachnoid space, and in the second case it revealed thick pus from which Bacillus coli was cultured. Both patients were operated on, and in both an epithelial tube was found which led downward from the dimple to the dura mater. Infected material had forced its way down this tube, giving rise to a subdural abscess, which was opened and drained. Both children made complete recoveries.

Reports of 5 similar cases were collected from other clinics and from the literature. In 2 instances pyogenic meningitis occurred. Laminectomy and drainage were carried out in both cases; one patient recovered, and the other died because of inadequate drainage. Two others had abscesses about the dura mater; both recovered. The fifth patient was not operated on.

The cases of 2 other infants were reported in which the dimples were noted shortly after birth. In both cases the sinuses were excised before any neurologic symptoms developed.

DISCUSSION

Dr. Peter Bassoe: Was the case referred to as having been reported by Clark the one reported by Samuel N. Clark, of Jacksonville, Ill., in the *Journal of Nervous and Mental Disease* in 1918?

Dr. Paul C. Bucy: Yes.

Dr. Peter Bassoe: I knew that patient. She was a girl, aged 13 years, who came to the Central Free Dispensary when Dr. Clark was working there. There was a dimple with a hairy tuft in the neck, but there was no sign of infection. Clumsiness of the fingers with hyperextensibility was present, but there was no sign of any disease of the long tracts of the spinal cord. In the cases observed by Dr. Bucy and Dr. Walker the infection produced severe symptoms referable to the spinal cord, so it seems that when there is no infection the symptoms may be slight. It was stated that the guinea-pig that was used for inoculation in the first case died. Did it have tuberculosis?

Dr. R. P. Mackay: There is good reason to believe that the process which Dr. Bucy so well illustrated (i. e., the failure of proper formation of the raphe in the embryo) is also at the basis of syringomyelia. I wish to ask whether there were any signs of an associated syringomyelia in these cases. I was interested to hear that in the first case there was some paresthesia in the arm, although the dermal sinus was at a lower level. There is perhaps a possibility of dysraphia in the spinal cord in the inferior cervical segments to account for this symptom.

I think that the relationship between the conditions Dr. Bucy described, spinal bifida and syringomyelia, is now better understood than it was formerly. Possibly when these various disturbances of the median dorsal raphe have been correlated it will be discovered that they are all pathogenically the same disease, with dermal, mesodermal (spina bifida) or intramedullary manifestations. Many intramedullary tumors appear to arise from heterotopic inclusions in the spinal cord at the time of the improper closure of the medullary groove.

Dr. Theodore T. Stone: What is known about the cause of ordinary spina bifida occulta cervicalis as seen in adults? Is there any relation between that type of case and the type that was reported?

Dr. Paul C. Bucy: In reply to Dr. Bassoe's question about the guinea-pig, I do not know what examinations were made, as I did not see the animal.

In answer to Dr. Mackay, so far as I know none of the patients I have seen has shown symptoms of syringomyelia. They were very young children, and it would be difficult to come to a conclusion whether there were any such signs. In the patient of Dr. Phemister, a child 13 or 14 years of age, there were no symptoms or findings. However, there is no question that symptoms of syringomyelia may occur in association with spina bifida, particularly in the cervical region (Turnbull, F.: *Brain* **56**:304, 1933).

In view of the fact that the paresthesia in the upper extremities disappeared immediately following the operation it does not seem likely that it was due to any intramedullary process such as syringomyelia. This symptom in the upper extremity can be rationally explained in another manner. I believe that the earlier illness, diagnosed as tuberculous meningitis, was in fact sterile meningeal inflammation or meningismus brought about by the close approximation of the subdural abscess to the subarachnoid space and that the paresthesia was a manifestation of a more chronic process of the same character, which involved the arachnoid membrane and the posterior spinal roots in the lower part of the cervical region.

There is certainly a close developmental relationship between congenital dermal sinuses and spina bifida cervicalis. The latter may not, however, be associated with such a sinus except in a few instances, such as that reported by Clark (*J. Nerv. & Ment. Dis.* **48**:201, 1918).

ENCEPHALOGRAPHY IN CHILDREN. DR. A. EARL WALKER (by invitation).

A short history of encephalography was presented, and the indications and contraindications for the procedure were discussed. The postencephalographic findings in the blood and in the spinal fluid were shown graphically. The encephalographic findings in the various types of mental retardation and infantile palsies were illustrated by lantern slides. Several encephalograms of patients suffering from degenerative diseases of the central nervous system were also shown. (The paper was published in full in the *American Journal of Roentgenology and Radium Therapy* [**32**:437, 1934].)

DISCUSSION

DR. JOHN FAVILL: What do you consider is the mechanism of absorption of spinal fluid in the young children of this group? May not the total absence of air over the cortex in the case of hydrocephalus have more significance than was given to it, as it appears to show an obstruction to the usual absorption channels?

DR. W. C. MENNINGER: Recently, at the meeting of the Central Neuropsychiatric Association in Cincinnati, the question was discussed briefly, and three of those present, including myself, gained a good deal of satisfaction in confessing that we felt a certain amount of panic during every one of these operations. I wish first to ask about the technic. Dr. Walker said that he uses general anesthesia, but I wish to know whether he also uses sodium amytal or other sedation prior to the anesthesia. Second, he said that he withdrew all the fluid he could, which I think is what every one tries to do, but this varies over such wide ranges that I should like to know the average amount withdrawn.

DR. ABRAHAM ETTLESON: Concerning the explanation given by Dr. Walker of cortical scarring producing enlargement of the lateral ventricle on the side where the choroid plexus was coagulated, I wish he would explain this more fully.

DR. HANS H. REESE: At the Wisconsin Psychiatric Institute encephalography is constantly performed under the supervision of Dr. William J. Bleckwenn. In several hundred patients, ranging from 3 months to 62 years of age, it has never been necessary to resort to general anesthesia. The patients are prepared for operation by the administration of codeine sulphate (from ½ to 1 grain [0.032 to 0.065 Gm.]) hypodermically or phenobarbital (from 5 to 10 grains [0.26 to 0.65 Gm.]) orally. Frequently the first encephalogram of an epileptic patient did not give an explanatory picture, but on repetition of the procedure an etiologic factor could be determined in the form of internal hydrocephalus, adhesive arachnoiditis, cortical disfiguration or a developmental or traumatic cerebral defect.

I agree with Dr. Walker that in neuropsychiatric diseases of childhood encephalography is necessary, because only by that procedure can one determine and explain clinical syndromes and intellectual and mental peculiarities with retardation. Encephalography enables one often to forecast the prognostic features and the advisability of further therapeutic efforts.

Whereas at the Wisconsin Psychiatric Institute Bleckwenn's closed system technic (double puncture graduated tube) is the procedure of choice for adults in order to permit complete drainage of the fluid, the simple lumbar puncture with

the three way stopcock is preferred for children. An effort is always made to drain the system as completely as possible under constant control of blood pressure, of rate and quality of pulse and respiration and of general reactions. The great fluctuations in peripheral leukocytic counts that Dr. Walker has presented have not been observed. Could they have been conditioned by the agent used for the general anesthetic and therefore be explained as a physiologic phenomenon of the dermatosplanchnic reflex alternation?

The greatest attention prior to encephalography should be devoted to metabolic dysfunction, especially that referable to the pancreas and adrenals. One of the patients at the institute in whom encephalography activated a latent hypo-insulinism, and in whom the diabetic coma could not be influenced, died. A labile constitution, especially in a child, must be carefully investigated before an encephalogram is made.

Whereas the therapeutic results in epileptic adults have been satisfactory and often encouraging in the series of patients at the institute, less beneficial results have been seen in epileptic children from one or even several encephalographies.

The first picture of Dr. Walker's series with the distinct, pallisade-like unilateral atrophy should be investigated in view of the history of the case. The condition may be Pick's disease. The lack of air in the subarachnoid spaces over the hemispheres may explain the marked bilateral internal hydrocephalus in some of his cases on the basis of a plastic arachnoiditis. In these cases repetition of the procedure is advised before any definite conclusions are reached.

DR. A. EARL WALKER: In answer to the question regarding the mechanism of absorption of spinal fluid, I think that it is generally agreed that this is absorbed through the arachnoid villi and pacchionian granulations and in some cases through the supracortical veins and some through the perineural spaces along the cranial and spinal nerves.

Absence of air over the cortex in hydrocephalus may indicate arachnoidal adhesions over the cortex, but this was not true in the patient I showed as operation revealed a normal subarachnoid space.

Regarding the increased size of the ventricle following cauterization of its choroid plexus, I have no explanation for that except that in children a localized cortical injury occurring to one hemisphere results not, as in adults, in a local outpouching of the ventricle but in a generalized ventricular dilatation on that side. I think that the enlargement of the ventricle on the one side was due to the trauma produced at the time of the cauterization.

Practically all of the encephalographies reported on this evening were performed under ether anesthesia. The patient is kept under light surgical anesthesia during the entire procedure and is taken immediately to the x-ray room; a small amount of anesthetic is given there if necessary. If a general anesthetic is used the fall in blood pressure and the feeble pulse are not so marked as if the procedure is carried out under local anesthesia, with or without codeine or morphine.

In all cases as much fluid is removed as one is able to obtain, the Bleckwenn technic with double lumbar punctures being used. At the same time the head is manipulated, moved from side to side, backward and forward, and an attempt is made to obtain as much fluid as possible, both from the ventricle and from the subarachnoid space. In children from 80 to 100 cc. is usually obtained. However, some encephalograms have been made with as little as 50 cc.

In the cases which I have studied, leukocytosis of the blood occurred constantly following encephalography. The patients were not all children but included several adults, and for the adults various other types of anesthetics were used. The majority of the patients were given avertin, but in some cases sodium bromide and chloral hydrate alone were used as premedication. In these cases, too, leukocytosis was noted.

I wish to thank Dr. Reese for his discussion. I also think that if the head were sufficiently manipulated air would be noted in the subarachnoid space in many cases in which it had not been seen. In these there may be adhesions entrapping the fluid, or the subarachnoid space may be normal but not filled with air for some as yet unknown reasons.

TREATMENT WITH DI-NITROPHENOL IN CASES OF DEMENTIA PRAECOX. DR. ISIDORE FINKELMAN and DR. W. MARY STEPHENS.

The mental and physical reactions to the administration of di-nitrophenol of 12 patients with dementia praecox have been studied. The average increase in the rate of oxygen consumption was 37.16. The average loss of weight was 1.44 pounds (0.7 Kg.) per week. Two patients with fat distribution of the hypopituitary type did not respond to di-nitrophenol with either loss of weight or increased oxygen consumption. The rates of oxygen consumption returned to the pretreatment values after the administration of the drug was discontinued. The nonprotein nitrogen and icteric index increased, and the blood cholesterol decreased during treatment. The icteric index and the cholesterol showed a tendency to return to pretreatment values, but the nonprotein nitrogen remained increased. Five patients improved mentally. The increased attention given the patients during treatment cannot be ruled out as having been the chief agent in causing the mental improvement. The reactions of patients with dementia praecox to the administration of di-nitrophenol together with oxygen should be studied.

DISCUSSION

DR. H. I. DAVIS: I wish to ask Dr. Finkelman if he has investigated the effect of di-nitrophenol on persons who are not suffering from dementia praecox. Is he acquainted with its effect on increased oxygen consumption, loss of weight, etc.?

I also should like to ask what is meant by dementia praecox and whether di-nitrophenol is not going to join the multitude of other drugs that have been used in the treatment for dementia praecox without any apparent results.

DR. CLARENCE A. NEYMANN: I have treated 2 patients with di-nitrophenol. One was a woman with schizophrenia who had been institutionalized for about twelve years. She showed marked introversion and indifference. Treatment was started with 1 grain (0.064 Gm.) daily and was gradually increased to 5 grains (0.32 Gm.) daily and was continued for seventeen days. At the end of that time the basal metabolic rate had increased from —8 to +45; probably because of lack of skill and overdosage the temperature rose to 103 F. The urine had the typical yellow color of di-nitrophenol. The patient became disturbed. She had not had active hallucinations for years, but now auditory and visual hallucinations developed. Therefore the treatment was discontinued. Three weeks later she had relapsed into her former lethargic state, and mental examination showed that she was no different than before the treatment was started. Incidentally this patient had a large appetite during the time when di-nitrophenol was administered. She was given as much food as she wished to eat. At the end of the febrile period she weighed 5 pounds (2.3 Kg.) more than she had before treatment.

The second patient, about 26 years of age, had schizophrenia of the simple type and had been ill since she was 16. Di-nitrophenol was given in doses of 1 grain at the beginning and the dose was gradually increased to 3 grains (0.195 Gm.) daily. The basal metabolic rate increased from —10 to +20. During the period of treatment she became excited and struck her mother. Later, after the di-nitrophenol was discontinued, she relapsed into the former state of lethargic indifference.

Years ago, at the Henry Phipps Psychiatric Clinic, injections of nucleic acid were given in similar cases. The reaction observed during the administration of di-nitrophenol was similar to that observed following the use of nucleic acid.

I wonder whether the psychic changes observed during treatment for schizophrenia do not correspond relatively with the changes in the average person when stimulated by an external trauma.

DR. CHARLES F. READ: As I see it, Dr. Finkelman's attempt has been to investigate the response of the organism as a whole in a person who is exhibiting symptoms of dementia praecox. This is an effort to determine the ability of the organism to respond normally, or as the average organism does, to such stimulation; in other words, to perform an experiment in vivo rather than to discover something in cadavers. It seems to me that the investigation of schizophrenia must take this route and continue to do so. Even though no great attempt is made

to discover a remedy, one may at times find some particular agent, biologic or otherwise, to which these organisms may respond more definitely than does the average so-called normal person.

I appreciate Dr. Finkelman's conservatism in reporting on the mental states of these patients before and after the treatment. He acknowledges that what improvement was noted was probably due to the increased interest shown in the patient, which is a type of psychotherapy.

Dr. Hans H. Reese: Research in schizophrenia should be encouraged, especially as the investigation is so carefully conducted and supervised under Dr. Read's guidance. That the nitrates of phenol may be extremely dangerous in certain persons is shown by numerous reports in the literature. The danger lies in the production of a blood dyscrasia similar to those following benzene intoxication or agranulocytosis. In view of such possibilities the nitrates of phenol should be used only in clinics, hospitals and institutions, and not in ambulatory cases. I recommend that permission be obtained from relatives prior to the administration of this drug. Dr. Finkelman should be encouraged to continue his interesting work, but I recommend continuous blood counts on all patients so treated in view of the increase of the icteric index even on discontinuance of the drug.

Dr. Isidore Finkelman: In reply to Dr. Reese, I am well aware of the dangerous character of this drug if it is not rigorously controlled. I do not advise its use in obese persons, but when one is confronted with incurable conditions the dangers of the drug should receive less relative consideration than when one uses it for a benign condition. The drug was not used for therapeutic research, however, but to see what the reactions of these persons were since the reactions of normal persons have already been reported. It was used in the cases of some nurses who were eager to reduce. One of them actually lost 55 pounds (24.5 Kg.). I fully agree, and I wish to emphasize, that one should not use this drug without making careful blood counts every day and numerous laboratory examinations; it should not be used at all for ambulatory patients.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Oct. 18, 1934

Albert W. Stearns, M.D., *Presiding*

Studies in Multiple Sclerosis: IV. "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction. Dr. Tracy J. Putnam.

This article was published in full in the May issue of the Archives, page 929.

The Blood Coagulation in Cases of Multiple Sclerosis. Dr. Philip Solomon and Dr. Benjamin Simon.

The reaction of the blood clotting time to (1) typhoid vaccine administered intravenously and (2) epinephrine administered subcutaneously was determined in 12 patients with multiple sclerosis and in 14 controls. The control group comprised 5 patients with epilepsy, 5 with psychoneurosis and 1 each with postencephalitic parkinsonism, tumor of the brain, neuromuscular dystrophy and syringomyelia. A modification of the Howell method was used in determining the clotting time.

1. In the experiments with typhoid vaccine the degree of the maximum decrease in the clotting time was not significantly different in the two groups of patients, averaging twenty-three minutes, or 54 per cent, in the group with multiple sclerosis, and seventeen minutes, or 47 per cent, in the control group. The duration of the fever was thirty hours in the former group and twenty-seven hours in the latter. There was a striking difference in the duration of the decrease in the clotting

time, the average duration being sixty-nine hours in the group with multiple sclerosis as contrasted with twenty-six hours in the control group.

2. In the experiments with epinephrine there was a marked difference in the two groups in regard to both the degree and the duration of the decrease in the clotting time. The average maximum decrease in the group with multiple sclerosis was nineteen minutes, or 45 per cent, as contrasted with four minutes, or 11 per cent, in the control group. The average duration of the decrease was three and seven-tenths hours in the former group and one hour in the latter.

DISCUSSION OF PAPERS BY DR. PUTNAM AND DRS. SOLOMON AND SIMON

DR. S. COBB: I wish to compliment the speakers on their clear and simple presentation. In regard to Dr. Putnam's article, it is hard to recognize an artery from a vein in the specimens into which injections are made. The only way is by the angle of the small side branches. Has Dr. Putnam any idea of the actual mechanism of embolism? When an artery is occluded there seems to be more complete necrosis, yet with occlusion of venules there is a sparing of the axons. Is that because in the former case there is a greater anoxemia, whereas in the latter there is a less complete and therefore more chronic process?

DR. J. B. AYER: There is one requirement which I am not satisfied that Dr. Putnam has fulfilled. How does he explain alternate improvement and relapse in human beings? Is it because the smaller thrombi are absorbed and the myelin is reinstated? How about patients with fixed lesions? Am I right in assuming that in these fixed lesions in the end, not only the myelin sheath disappears but also the axons?

DR. F. FREMONT-SMITH: I wish to ask Dr. Solomon a question in regard to the response of the blood to these two procedures, injection of typhoid vaccine and of epinephrine. It seems to me of utmost importance. I wish to know whether any appreciable number of the controls showed a curve that would fall into line with that of the patients with multiple sclerosis or vice versa. Had any of the individual patients with multiple sclerosis presented normal curves?

DR. LESTER KING: I wish to ask about gliosis. Why does one secure active glial proliferation, whereas in subacute forms there is no gliosis? Is there some other factor, apart from venous thrombosis, that will cause considerable proliferation of glia?

DR. H. VIETS: I realize the importance of this work and of the disease. Thinking back to Dr. Putnam's presentation four years ago, I am personally not quite so convinced tonight as I was at that time. The more I see of these slides, the less convinced I am that they resemble the picture of multiple sclerosis in human beings and the more they seem to resemble the demyelinization of other diseases.

DR. B. SIMON: In our series of 12 patients, 1 control subject in the group given epinephrine and 1 in the group given typhoid vaccine reacted like a patient with multiple sclerosis. All others reacted as noted on the graph. Of the patients with multiple sclerosis, 5 of 12 in the group given typhoid vaccine fell in the borderline or reacted like controls. All of the patients with multiple sclerosis reacted to epinephrine in a typical fashion. In regard to clotting time, we have always had trouble with the nomenclature of the clotting time. A decrease in the clotting time and decreased clotting are confused. For example, an average person will show a clotting time of twenty minutes, and in response to epinephrine this will drop to fifteen minutes. The coagulability is increased, but the coagulation time is decreased. Blood clots more quickly and is therefore much more likely to form a thrombus. In regard to Dr. Viet's question, the notion about thrombosis is that it is merely a mechanism; many things may cause it. Rapid pulse rate and increased blood pressure are associated with the administration of epinephrine and with fever. In studying postoperative thromboses, Heusser showed that postoperatively the blood platelets agglutinate much easier. Starlinger came to this conclusion, and Budde and Karten corroborated this. König found that the disintegration of platelets increases the tendency to clot. After extirpating the spleen,

products that cause a fall in platelets reverse and cause an increase. The resistance of the platelets follows in the same direction. König performed some experiments with epinephrine on rabbits and found decreased clotting time. We can show nothing more than is seen on the graphs; we cannot make any interpretation beyond the fact that these changes are associated with the injection of typhoid vaccine and of epinephrine in some cases of multiple sclerosis. The change in the coagulation power of the blood is not seen in 100 per cent of cases. We do not think that it should be used as a diagnostic procedure.

DR. J. B. AYER: Have patients been examined in periods of relapse?

DR. P. SOLOMON: We have taken them as they came. If our views are correct, of course, typhoid vaccine therapy is definitely contraindicated.

DR. T. J. PUTNAM: I wish to ask Dr. Viets what aspect of the experimental lesion was deficient.

DR. H. R. VIETS: The lesion in general seems more diffuse and not so circumscribed as in cases of multiple sclerosis. This appears to be most evident in the last two slides shown.

DR. T. J. PUTNAM: The slides from the human material were not shown as a proof of my impressions in regard to the pathologic picture of the disease, but rather as an example of the method by which the problem might be approached. As to the point that the lesions in animals are less clear than those in human beings, I think that the clearcut character of the lesions in human beings has been overemphasized. Perhaps the majority, especially those in the cerebral white matter, have indistinct margins and still contain remains of myelin. Of course, plaques can never be as large in an animal as in man, and this will have some effect on the intensity of the process, but if one analyzes the essential features of multiple sclerosis I think that one will find them reproduced in these animal experiments.

Closure of an artery, for example by embolism, causes intense anoxemia with loss of axis-cylinders as well as of myelin. To be sure, many lesions of this kind exist in cases of multiple sclerosis in human beings, as can be satisfactorily shown only by the use of a special technic which permits the employment of different specific stains in the same block. In general, the milder the injury the more the myelin suffers as compared with the axis-cylinders.

I doubt if myelin is ever regenerated. At least there was no apparent tendency to regeneration in the first series of experimental animals. Further, there are no Schwann cells to replace the myelin in the central nervous system. Dr. Morrison has produced evidence that myelin is laid down by the embryonic oligodendroglia, which no longer exist in the adult brain. I believe, however, that the axis-cylinders can function even when deprived of myelin. Thus, one sometimes finds almost or a whole optic nerve has become demyelinated and yet the patient has had some vision.

Gliosis takes time to develop, at least several months, and this is probably the reason that it does not occur in acute lesions. I have the impression that it continues to progress, certainly until all of the products of degeneration have been removed. In certain states of disturbed nutrition, as in pernicious anemia, gliosis may fail to occur until the missing factors are supplied.

CORRECTION

In the article on Constantin von Monakow by Dr. Colin K. Russel in the May issue (ARCH. NEUROL. & PSYCHIAT. **33**:1088, 1935), two lines were dropped at the bottom of page 1089. The sentence beginning "The years 1869 and 1870 he and his . . . ." should continue as follows: ". . . . father spent in Paris, where, while continuing his studies, he became interested in the theater and attended a private conservatory for dra-"

Book Reviews

The Nature and Treatment of Amentia. By L. Pierce Clark. Price, $4.25. Pp. 306. Baltimore: William Wood & Company, 1933.

Most studies of mental defect have confined themselves to a description of the behavior of the defective person, of diagnostic criteria and of the organic pathology. In this book Dr. Clark has attempted to go further. An organic defect of the central nervous system—whether congenital or acquired—must affect the dynamic expression of the instinctual life. Dr. Clark's investigation has centered on an attempt to understand the defective person's behavior as an expression of instinctual urges and to apply therapeutic methods based on this understanding. In the introduction he gives a short and schematic description of psychoanalytic concepts. This introduction is inadequate for the reader who has slight or no acquaintance with psychoanalysis and is unnecessary for those who are psychoanalytically trained. The introduction is followed by a number of reports of cases ranging from those of idiocy to those of borderline states. These reports and the summarization of the material are of great interest, as are the suggestions for therapy. The more intelligent the defective patient the more does Dr. Clark rely solely on psychoanalytic therapy.

This book is stimulating, and the approach to the discouraging field of mental defect is worthy of consideration and further research. Neither the methods nor the conclusions can be accepted in toto at present. Particularly, further research is required to test the validity of the concept that feebleminded persons can be improved by psychoanalytic therapy. There seems to be no question, however, that the lives of these people may be made more tolerable by the use of psychoanalytic knowledge in their care and training.

A Handbook of Psychiatry. By John H. Ewen, M.R.C.P. (Edinburgh), D.P.M. Price, $4.75. Pp. 267. Baltimore: William Wood & Company, 1934.

The purpose of Ewen in publishing this book is not to furnish a textbook. It is his intention that an orderly and methodical presentation of salient facts concerning the subject of mental disorder be made so as to supply a source for rapid reference. He has succeeded well in compiling in a book of approximately two hundred and sixty pages an excellent system of outlines of the different clinical forms of psychiatric illness or disorder. The book is little more than a definite outline. There is practically no discussion, except a few explanatory sentences which define the headings. The outlines are detailed and inclusive. For this reason it is accurately titled "A Handbook of Psychiatry" rather than a text.

The authors quoted are largely British or continental, although Ewen shows thorough familiarity with psychiatric literature in general. The last two sections, one on the legal relations of mental disorder, and the other an appendix, with a discussion of various medicolegal aspects of psychiatry, are based on material derived from the English law and practice and therefore are of little use to American readers.

La sympathicothérapie. By P. Gillet. Paper. Price, 38 francs. Pp. 262+, with 3 illustrations. Paris: Gaston Doin et Cie, 1934.

By stimulating the nasal mucous membrane with a probe it is possible to secure remarkable therapeutic results in cases of asthma, angina pectoris, tabes, trigeminal neuralgia, chronic rheumatism, poliomyelitis, spastic paraplegia and hemiplegia, according to the author. The principle employed is similar to that of the acupuncture of early Chinese times (B. C. 2600), osteopathy, chiropractic, Abrams' treatment, and centrotherapy. Those interested may read further details in the original.

A Field Study of the Behavior and Social Relations of Howling Monkeys. By C. R. Carpenter. Comparative Psychology Monographs, volume 10, no. 2, serial no. 48. Price, $2.25. Pp. 168, with 16 illustrations. Baltimore: Johns Hopkins Press, 1934

Dr. Carpenter reports an interesting naturalistic study of howling monkeys, with unusually complete data on social behavior and organization.

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